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and
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Millennium Meeting
Cardiff, 23–26 May 2000

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The British Journal of Surgery

The Journal is specially related to the Association of Surgeons of Great Britain and Ireland, the Surgical Research Society, the Vascular Surgical Society of Great Britain and Ireland, the British Association of Endocrine Surgeons, Eurosurgery, the Surgical Infection Society (Europe), the European Society of Surgical Research and the Association of Surgeons of the Netherlands

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Candidates must be residents of the United Kingdom or the Republic of Ireland, but need not be either Fellows or Affiliate Fellows of the Association; however, they should be engaged in general surgery or in a sub-specialty thereof. A full Curriculum Vitae should be submitted, giving details of past and present appointments and publications, together with a detailed account of the proposed programme of travel, costs involved and objectives to be achieved. Shortlisted candidates will be interviewed by the Scientific Committee of the Association, at 2.00pm on 20 November 2000, who will pay particular attention to originality, scope and feasibility of the proposed journey. The successful candidate will be expected to act as an ambassador for British and Irish Surgery, and should be fully acquainted with the aims and objectives of the Association of Surgeons in its role in surgery. After the visit, the successful candidate will be asked to address the Association at its Annual General Meeting.

Deadline for applications: **Monday 2 October 2000**
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Only Fellows including Full, Senior, Associate and Affiliates of the Association of Surgeons may apply and, if successful, a grant will be made available to individual applicants.

Deadline for applications: **Monday 2 October 2000**

Further details are available from Mrs N Lewis, The Association of Surgeons of Great Britain and Ireland, at the Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London WC2A 3PN. Tel: 020 7973 0300 Fax: 020 7430 9235.

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Association of Surgeons of Great Britain and Ireland and Surgical Research Society

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The combined meeting of these societies occurs in Cardiff this year and the *British Journal of Surgery* continues its association with these two of its affiliated societies in the production of this abstract supplement.

The *BJS* is pleased to see a further collaborative meeting but is aware of discussions occurring between the Surgical Research Society, the Society of Academic Surgeons and the Association of Surgeons of Great Britain and Ireland. Groupings and affiliations may change and develop. However, the *BJS* will remain responsive to these changes and will continue to strive to produce journals and supplements that reflect the activities of these groups.

The Editors of the *BJS* wish all participants an enjoyable and fruitful meeting in Cardiff.

The Editors
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Specialist Procedure related courses - These courses are 2-3 days long and concentrate on specific clinical situations that are particularly relevant to a speciality and focus on specific endoscopy operation(s).

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Ductal Calculi: The Laparoscopic Approach ***27th - 28th March 2000***
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SURGICAL SKILLS UNIT

Essentials of Laparoscopic Surgery

16th - 18th February 2000
3rd - 5th April 2000

A 3 day practical course designed for those starting to operate using a laparoscope. This course covers the essential skills and safety procedures for basic laparoscopic operations such as laparoscopic cholecystectomy or laparoscopic appendectomy

The emphasis is on "hands on" experience using specially designed tissue simulations. The course includes an extensive handbook covering essential theoretical knowledge which is provided before the course. This allows more course time to be spent developing practical skills.

The course provides

- "hands on" experience using simulators
- live operative demonstration
- clear explanation and guidelines
- skills assessment and checklist
- small group discussion

Call for further details

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ADVANCED COURSES IN DUNDEE

Ductal Calculi: The Laparoscopic Approach

27th - 28th March 2000

Faculty: **Sir A. Cuschieri** **Mr S. Shimi**
Mr A. H. M. Nassar **Miss Peta Dunkley**

A 2 day laboratory based course designed for surgeons who have mastered laparoscopic cholecystectomy and wish to progress to single stage managements of ductal calculi at the time of laparoscopic cholecystectomy.

The course covers the management issue as well as essential endoscopic skills required such as cannulation of common bile duct, choledocoscopy and stone extraction. The emphasis is on relevent skills training using specially designed tissue simulations

Live recorded video will be used to illustrate the application of these skills

The practical course offers;

- experienced tutors
- small group tuition
- intensely practical programme
- 'hands on' practical sessions
- live theatre link (when possible)
- practical hints
- troubleshooting

Course fee excludes accommodation but includes all course materials

Fee: £640

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ADVANCED COURSES IN DUNDEE

Practical Aspects of Laparoscopic Fundoplication

13th - 15th March 2000

Faculty: **Sir A Cuschieri** **Mr S Shimi**
Mr A Munro **Miss Peta Dunkley**

This three day course covers the practical and clinical aspects of both partial and total laparoscopic fundoplication. The course has a small group format and personal tuition is available during the practical simulation sessions.

The practical course offers;

- experienced tutors
- small group tuition
- intensely practical programme
- 'hands on' practical sessions
- live theatre link (when possible)
- practical hints
- troubleshooting

Course fee excludes accommodation but includes all course materials

Fee: £950

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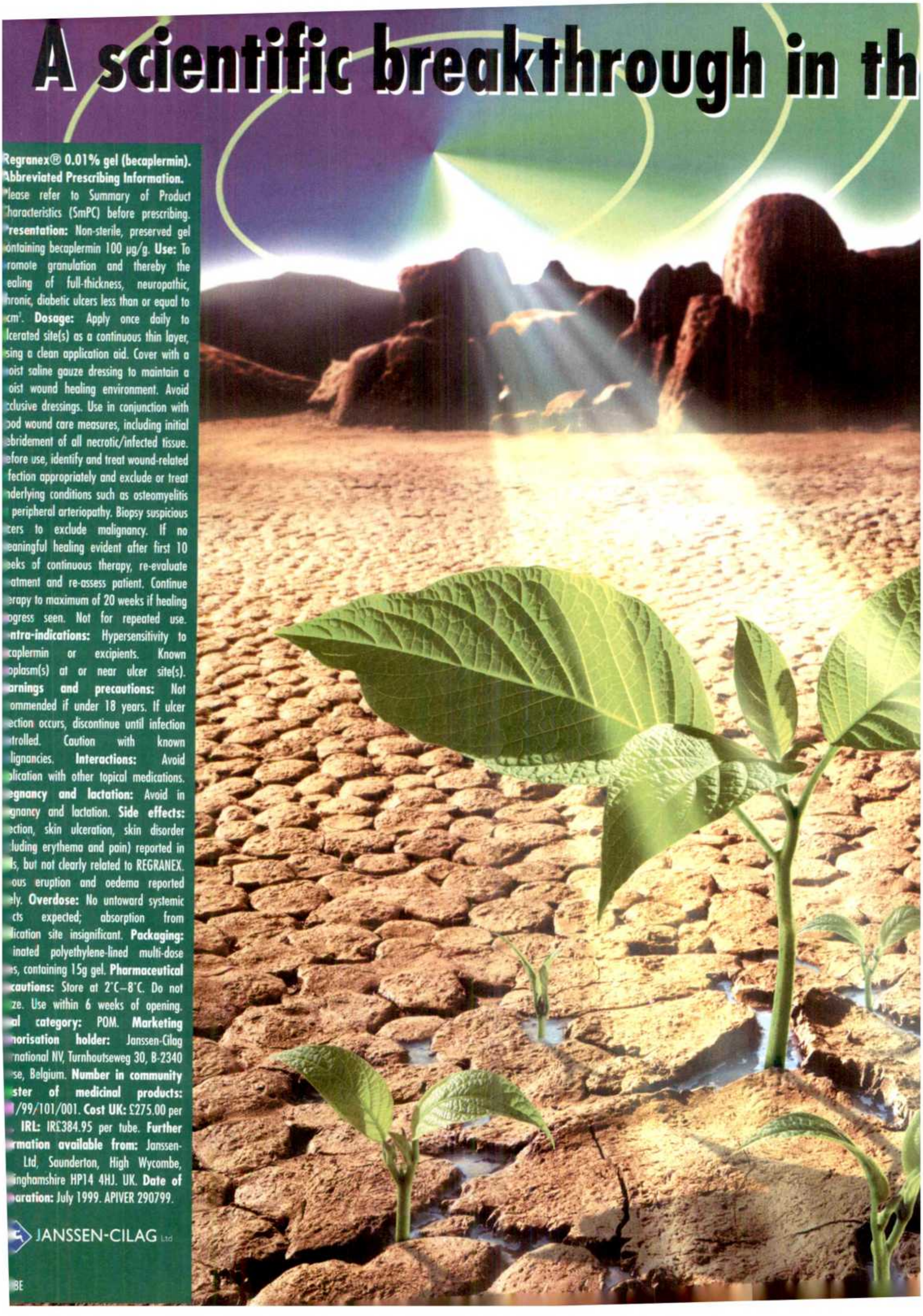
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Periodic assessment of
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d. Discontinue if bleeding
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superinfection. Convulsions
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st frequent: gastro-intestinal
s; various skin reactions
shes, erythema, pruritus and
lergic reactions; superinfec-
bitis, thrombophlebitis,
nation at site of injection.
t: muscle pain or weakness;
n; dry mouth, stomatitis,
edema; tiredness and rarely
interstitial nephritis.
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en reported. Overdose:
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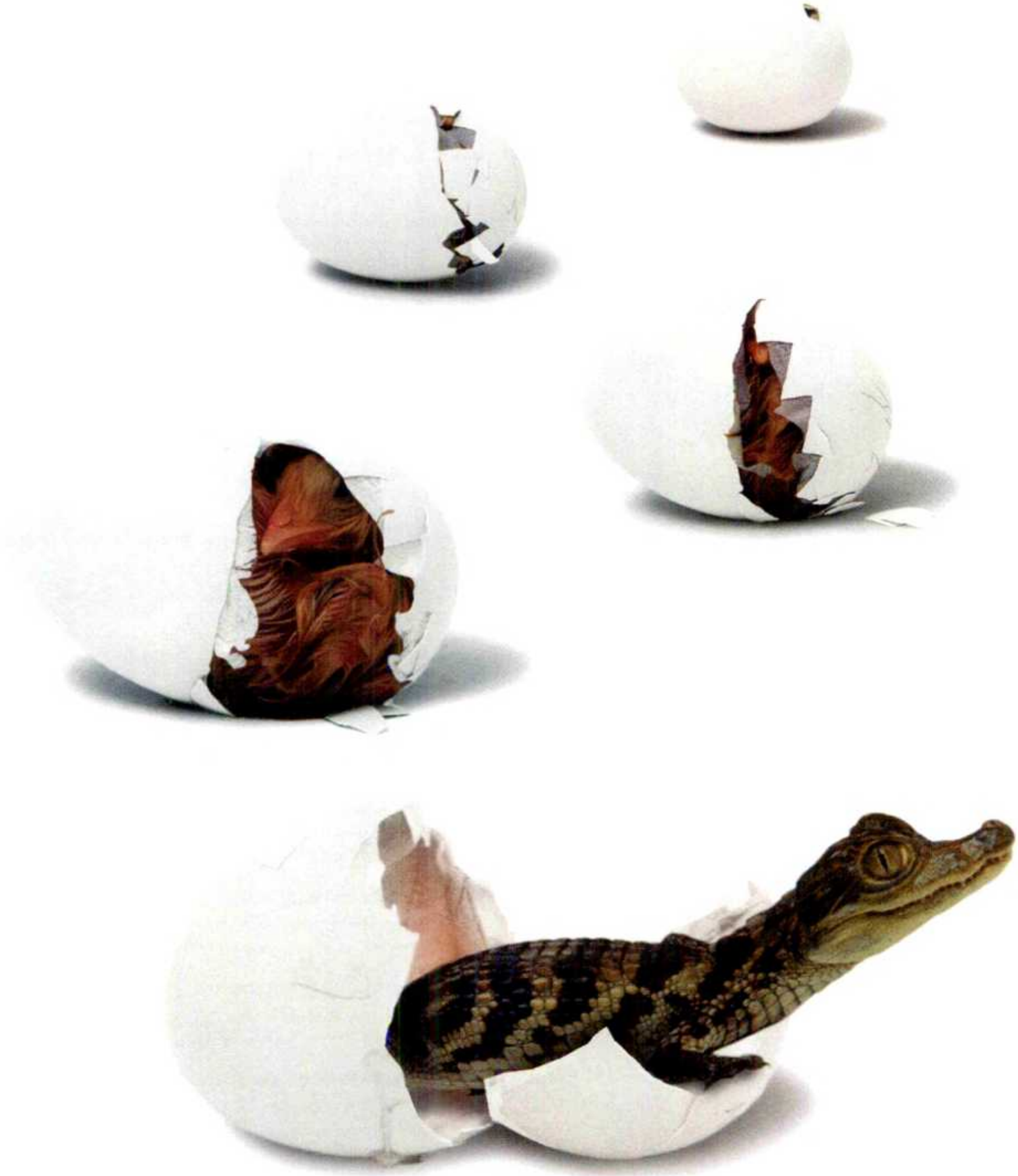

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CONFIDENT CHOICE for nosocomial infections

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PRESENTING AND WRITING-UP YOUR RESEARCH

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This course is organised annually by Professor Andrew Nicolaides and Mr George Geroulakos and the team of the Irvine Laboratory at St Mary's Imperial College. Its aim is to fulfil the need of many academic staff, research assistants and postgraduate students undertaking higher degrees such as MSc, MPhil, PhD on how to get the maximum and highest possible quality of publications out of their research. Delegates are welcome to bring any special problems they may have for comments and advice from the members of the faculty.

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Writing a Research Grant Application. L. Cox, Research Contracts Manager (Medical), Imperial College, London

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Early registration is advisable, as places are limited and will be given on a first come, first served basis.

Patey Prize 001

Modulation of the hepatic export protein synthetic response to feeding in advanced pancreatic cancer

M.D. Barber, T. Preston, D.C. McMillan, J.A. Ross and K.C.H. Fearon *University Department of Surgery, Royal Infirmary of Edinburgh, SURRC, East Kilbride, University Department of Surgery, Glasgow Royal Infirmary, UK*

Aims: Accelerated hepatic export protein synthesis may contribute to wasting and poor survival in cancer cachexia. $n-3$ fatty acids (derived from fish oil) can modulate *in vitro* hepatic export protein synthesis and, thus, we measured the effect of $n-3$ fatty acid supplementation on this protein synthesis in the fed and fasting state in patients with advanced pancreatic cancer.
Methods: Albumin and fibrinogen synthesis were measured in the fed and fasting state in eight weight-losing pancreatic cancer patients and six healthy controls. Protein synthesis was measured by an intravenous flooding dose of labelled phenylalanine Tracer protein incorporation was measured by gas chromatography/mass spectrometry. Cancer patients were studied again after receiving an $n-3$ fatty acid-enriched nutritional supplement, providing 600 kcal and 2 g eicosapentaenoic acid per day for 3 weeks.
Results: At baseline, fasting albumin synthesis was not different between cancer patients and controls, and rose to a similar extent in the fed state (29 per cent *versus* 24 per cent, $P=0{\cdot}7$) Fasting fibrinogen total synthetic rate was about 300 per cent higher in cancer patients than in controls ($P<0{\cdot}005$) In cancer patients, fibrinogen synthetic rate rose further in the fed state (by 38 per cent), while, in controls, there was no significant change (14 per cent) In cancer patients, after 3 weeks of the $n-3$ fatty acid-enriched supplement, fasting albumin and fibrinogen synthesis rates were unchanged. In the fed state, however, albumin synthesis was no longer stimulated by feeding, and fibrinogen synthesis only increased by 17 per cent. Thus, after administration of the supplement, there was significant down-regulation of albumin and fibrinogen synthesis in the fed state, from 33 per cent overall initially to 10 per cent after intervention ($P=0{\cdot}012$).
Conclusions: Stimulation of hepatic protein synthesis by feeding in advanced cancer patients may explain the resistance to weight gain in cachexia. $n-3$ fatty acid supplementation abolished the stimulation of liver export protein synthesis in the fed state and may therefore allow supplied amino acids to be used for anabolism.

Patey Prize 002

Correlation of oestrogen receptor subtype with angiogenic activity in primary breast cancers

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Academic Surgical Unit, University of Hull, Hull, UK and Mater Misericordiae Hospital, Dublin, Ireland

Aims: The importance of oestrogen receptor (ER) status in primary breast cancer is widely accepted, though the role of the newly described ERβ and its clinical significance remain unclear Multiple angiogenic factors have been identified; in this study, we examined the relationship between basic fibroblastic growth factor (bFGF), platelet-derived growth factor isoforms (PDGF-A, PDGF-B) and expression of ER subtypes, ERα and -β.
Methods: Total RNA was extracted from 45 tumours and 1 µg used for semiquantitative reverse transcriptase polymerase chain reaction (RT-PCR) analysis using specific primers for bFGF, PDGF-A and -B, ERα and ERβ Reference standards were prepared and electrophoresced alongside the unknown samples. Using UVI band software, an arbitrary value of 100 was ascribed to the reference standard and the fluorescence intensity of the unknown expressed as a percentage of this standard.

Results:

	bFGF	PDGF-A	PDGF-B
ERα positive ($n=33$)	0 (0–37·1)	42·7 (0–120·0)	25·0 (0–111·2)
ERα negative ($n=12$)	26·3 (0–43·0)	34·4 (0–105·3)	33·3 (0–82·5)
ERβ positive ($n=20$)	18·3 (0–37·1)	60·1 (0–120·4)	45·7 (0–113·4)
ERβ negative ($n=25$)	0 (0–40·2)	22·7 (0–108·0)	12·8 (0–98·4)
Coexpression ERα/β ($n=18$)	18 (0–37·2)	60·9 (0–120·1)	44·4 (0–112·2)
Single ER subtype ($n=27$)	0 (0–43·1)	29·0 (0–102·5)	10·7 (0–88·3)

Data = median (range), arbitrary units

Both PDGF-A and PDGF-B were significantly elevated in $ER\beta^+$ tumours ($P=0{\cdot}016$, $P=0{\cdot}05$, Mann–Whitney) but only PDGF-B in those tumours which coexpressed ERα/β ($P=0{\cdot}05$, Mann–Whitney) Increased expression of bFGF was seen in $ER\alpha^-$ tumours ($P=0{\cdot}015$, Mann–Whitney) A strong positive correlation was observed between PDGF-A and PDGF-B ($P<0{\cdot}001$, Spearman's), and a positive but nonsignificant correlation between PDGF-A and bFGF expression ($P=0{\cdot}06$, Spearman's).
Conclusions: The results of this study demonstrate for the first time a relationship between increased angiogenic activity and expression of ER subtypes, where changes in relative expression of each receptor may be associated with angiogenic response. The relationship between angiogenic cytokines and steroid receptors – in particular, associations with the novel ER, ERβ – may have potential implications for therapeutic manipulation.

Patey Prize 003

Bactericidal/permeability-increasing protein attenuates acute lung injury in lower-limb ischaemia-reperfusion injury

D.W. Harkin, A.A.B. Barros D'Sa*, K. McCallion, M.I. Halliday and T G Parks **Vascular Surgical Unit, The Royal Victoria Hospital, Belfast, and Department of Surgery, The Queen's University of Belfast, UK*

Aims: Lower-limb ischaemia–reperfusion injury is associated with a remote gut injury and the resultant systemic endotoxaemia is believed to 'drive' the systemic inflammatory response syndrome and promote acute lung injury. We hypothesized that recombinant bactericidal/permeability-increasing protein ($rBPI_{21}$) would attenuate endotoxin-induced systemic inflammation and acute lung injury
Methods: Anaesthetized ventilated pigs underwent midline laparotomy and bilateral external iliac artery occlusion for 2 h, followed by 2·5 h reperfusion. They were randomized ($n=12$) to receive $rBPI_{21}$ ($2\,mg\,kg^{-1}$) or control protein thaumatin ($2\,mg\,kg^{-1}$) by intravenous infusion over the first 0·5 h of the reperfusion period. A control group ($n=6$) underwent laparotomy without further treatment. Blood from a carotid artery cannula was taken every 0·5 h for arterial blood gas analysis. Plasma was separated and stored at –70°C for later determination of plasma interleukin (IL)-6 by bioassay as a marker of systemic inflammation. The alveolar–arterial (A-a) gradient was measured using the formula [(A-a) gradient = fraction inspired $O_2 \times 710-(\text{arterial } pCO_2/0{\cdot}8)-\text{arterial } pO_2$]; it is a measure of lung function, with a large gradient indicative of impaired oxygen transport and, hence, lung injury.
Results:

Group	IL-6	Lung wet-to-dry ratio	(A-a) gradient
Control	430·54 (66·17)	5·79 (0·79)	183·19 (45·75)
IRI	1616·57 (390·84)*	9·32 (0·56)‡	407·97 (53·13)*
IRI + rBP_{21}	564·08 (272·00)†	7·13 (1·39)	246·65 (14·28)†

*$P<0{\cdot}005$ *versus* control, †$P<0{\cdot}01$ *versus* IRI, ‡$P<0{\cdot}01$ *versus* control Data represent mean (s.e.m.) Statistical comparison one-way ANOVA and Students' *t*-test

Conclusions: Treatment after ischaemia with $rBPI_{21}$ significantly decreases the IL-6 response to lower-limb ischaemia–reperfusion injury. Further, it significantly attenuates pulmonary oedema and maintains lung oxygen transport

Patey Prize 004

p16^{INK4} and p53 gene therapy results in pancreatic tumour regression *in vivo*

P. Ghaneh, W. Greenhalf, M. Humphreys, D. Wilson, N. Lemoine and J.P. Neoptolemos *Department of Surgery, University of Liverpool, Liverpool, UK*

Aims: Previous work has shown tumour suppressor gene therapy to inhibit pancreatic tumour cell growth but only *in vitro*. The aim of this study was to demonstrate regression of pancreatic cancer *in vivo* following tumour suppressor gene replacement therapy.
Methods: Replication-deficient recombinant adenovirus which expressed wild-type p53 or p16 under a CMV promoter was used for gene transfer to tumours. Identical vectors expressing either β-galactosidase or luciferase were used as the control. The human pancreatic cancer cell line MIAPACA was used to generate tumours in 8-week-old female nu-nu mice. Each mouse received an injection of 1×10^7 cells into each flank. Tumours were left to develop for 4 weeks. Each tumour then received one injection of 5×10^{11} virus particles for three consecutive days. Tumour volume was measured twice a week until the mice were killed after 3 weeks. Treatment groups (six animals) received intratumoral injections of virus expressing either p53, p16, β-galactosidase or luciferase. Tumours were removed from a single animal 44 h after injection, for expression analysis. RT-PCR was used to amplify the transduced gene in tumours.
Results: Wild-type p16 and p53 expression of RNA in the tumours was demonstrated using PCR. The ratios of change in tumour volume for each group were: mean [standard deviation], luciferase 3·9 [2·7], β-galactosidase 2·4 [0·9], p16 1·4 [1·6] and p53 1·5 [1·6] ratio units. There was a significant difference in tumour volume change between the treatment groups and the controls $P < 0{\cdot}01$ (Mann–Whitney *U*), but not between p53- and p16-treated tumours.
Conclusions: Tumour suppressor gene transfer produced significant regression of tumours in this animal model. These results indicate a role for tumour suppressor gene therapy in the treatment of pancreatic cancer.

Patey Prize 005

Thrombospondin (TSP): angiogenic role in early and advanced breast cancer

G.J. Byrne, K.E. Hayden, L. Tetlow, S. Drinkwater, A.H. Howell and N.J. Bundred *University Hospital of South Manchester, UK*

Aims: In cancer models, TSP has been shown to inhibit angiogenesis or promote metastasis by increasing adhesion of malignant cells to endothelium. To determine the role of TSP in breast cancer, we have measured TSP in plasma and tumour cytosols.
Methods: TSP was measured, by radio-immunoassay, in plasma (pTSP) and tumour cytosols (cTSP) of women with early breast cancer (EBC) ($n=71$). PTSP in EBC was compared with pTSP levels in women with advanced breast cancer (ABC) ($n=66$), normal controls ($n=77$), and was correlated with prognostic features and microvessel density (MVD) (measured by CD31 immunostaining). CTSP levels were compared with prognostic features, tumoral levels of CD31 and microvessel density.
Results: pTSP in women with EBC (median = 461, IQR = 346–844 ng mL^{-1}) and ABC (median 588, IQR = 401–904 ng mL^{-1}) were elevated when compared with normal controls (median = 227, IQR = 177–270) ($P < 0{\cdot}001$). Women with lymph-node metastases ($n=35$) had higher levels of TSP (median = 509, IQR = 411–997) than women who were node-negative (median = 297, IQR = 225–401) ($n=36$) ($P < 0{\cdot}05$). Levels of pTSP in EBC correlated with MVD ($r=0{\cdot}46$, $P < 0{\cdot}01$). Levels of TSP in tumour cytosols of women with EBC (median = 1714, IQR = 877–4559 ng mL^{-1}) correlated with tumoral levels of CD31 (median = 154 ng mL^{-1}, IQR = 10·28–32·93 ng mL^{-1}) ($r=0{\cdot}491$, $P < 0{\cdot}01$) and microvessel density ($r=0{\cdot}41$, $P < 0{\cdot}05$).
Conclusions: Plasma thrombospondin levels are a marker of metastatic disease in EBC and ABC, and may promote rather than inhibit tumoral angiogenesis.

Patey Prize 006

The biogenic amine, dopamine attenuates neutrophil–endothelial interaction: a novel role as an anti-inflammatory cytokine

S. Sookhai, J.H. Wang, D. Winter, W.O. Kirwan and H.P. Redmond *Department of Academic Surgery, Cork University Hospital, Cork, Ireland*

Aims: Activated neutrophil (PMN)–endothelial interaction is potentially deleterious. Previous work has shown that the biogenic amine, dopamine (DA) functions as an anti-inflammatory cytokine by inducing PMN apoptosis. We evaluated the effect of DA on PMN transendothelial migration and adhesion receptor expression, as well as on the endothelial molecules, E-selectin and ICAM-1.
Methods: PMNs were isolated from healthy controls, stimulated with lipopolysaccharide (LPS) and tumour necrosis factor-α (TNF-α) and treated with DA. CD11b and CD18 PMN adhesion receptor expression were assessed flow cytometrically. In a separate Transwell experiment, the effect of the chemoattractant peptide, IL-8, on PMN migration was assessed. Human umbilical vein endothelial cells (HUVEC) were stimulated with LPS/TNF-α, incubated with DA and ICAM-1, and E-selectin endothelial molecule expression assessed.
Results:

	Normal PMN	Stimulated PMN	Stimulated PMN + 10 μM DA	Stimulated PMN + 100 μM DA
Per cent PMN Transendothelial migration				
–IL 8	14 ± 1	40 ± 15*	7·5 ± 0·2*@	8 ± 0·25*@
+IL 8	25 ± 2·5	65 ± 16*	18 ± 2*@	20 ± 3*@
Adhesion receptor expression on endothelial cells and PMN				
E-Selectin	3·9 ± 0·4	8·1 ± 0·5*	4·3 ± 0·2@	3·7 ± 0·05@
ICAM-1	3·8 ± 0·2	9 ± 0·8*	4·3 ± 0·05@	4·6 ± 0·02@
CD11b	76·7 ± 2	252·5 ± 5*	174 ± 3*@	175·3 ± 4*@
CD18	139·4 ± 4	352·4 ± 5*	266 ± 4*@	219·7 ± 3*@

Data: mean ± s.d. Statistical analysis: ANOVA. *$P < 0{\cdot}01$ *versus* normal PMN. @$P < 0{\cdot}05$ *versus* stimulated PMN.

There was a significant increase in transendothelial migration in stimulated PMN as well as in CD11b/CD18 and endothelial E-selectin and ICAM-1 expression compared with normal PMN. DA attenuated these changes. The chemoattractant effect of IL-8 was also abolished.
Conclusions: These results identify for the first time that DA attenuates the initial interaction between PMN and endothelium, providing further evidence that it also functions as an anti-inflammatory cytokine.

Patey Prize 007

Platelet activation and platelet neutrophil conjugate formation in chronic lower-limb ischaemia

P.A. Coughlin, P.F. Jones*, E.P.L. Turton, R.C. Kester and D.J.A. Scott *Departments of Vascular Surgery and *Molecular Medicine, St James' University Hospital, Leeds, UK*

Aims: Platelets and their adhesion to leukocytes have the potential to promote inflammatory and thrombotic processes, and high levels of platelet neutrophil conjugates (PNCs) have been seen in acute cardiac ischaemia. This study sought to determine differences in platelet activation, neutrophil activation and, for the first time in lower-limb ischaemia, to determine PNC formation in varying severities of lower-limb ischaemia.

Methods: Sixty-two subjects were recruited; 15 patients with rest pain (nine men, six women), 35 patients with claudication (20 men, 15 women) and 12 age-matched controls (eight men, four women). Blood specimens were taken from an antecubital vein following a 1-h period of rest. Immunoflourescent monoclonal antibodies were used to determine platelet activation (P-selectin expression), neutrophil activation (CD11b expression) and PNC formation (CD11b, neutrophil marker; CD42b, platelet marker) Flow cytometric analysis was then performed on the labelled blood specimens. Percentage PNC formation was determined as the percentage of neutrophils with platelets bound to them.
Results: Values are shown as medians and interquartile ranges. Significance is taken as $P<0\ 05$ (Mann–Whitney *U* test).

	Rest pain	Claudicants	Controls
White cell count ($\times 10^9 L^{-1}$)	9 7 (7 95–10 45)*	8 2 (6 8–9 3)	7 7 (6 9–8 55)
P-selectin (MFI)	2 50 (1 82–4 03)†*	1 67 (1 30–2 02)	1 73 (1·50–1 99)
CD11b (MFI)	9 70 (8 19–11 88)	8 96 (6 36–10 90)	8 84 (7 19–10 10)
%PNC formation	8 92 (4 51–13 53)	4 87 (2 85–9 87)*	14 3 (5 77–20 50)

†$P<0\ 01$ *versus* claudicants, *$P<0\ 05$ *versus* controls MFI, mean fluorescent index

Conclusions: This is the first time that increasing severity of lower-limb ischaemia has been associated with platelet activation using platelet P-selectin expression as a marker of activation. Low-circulating PNC formation is associated with chronic lower-limb ischaemia. This is potentially owing to PNC adhesion to damaged endothelium, with the subsequent neutrophil migration causing subsequent tissue damage by the release of proteolytic enzymes and free radicals.

Patey Prize 008

Hypoxic pneumoperitoneum initiates the metastatic cascade in colon cancer cells

P.A. Paraskeva, D. Peck and A. Darzi *Academic Surgical Unit, Imperial College School of Medicine, St Mary's Hospital, London, UK*

Aims: Tumour cells when rendered hypoxic have an enhanced ability to form metastases The carbon dioxide (CO_2) pneumoperitoneum used in laparoscopic surgery as well as alternative gases such as helium (He) cause hypoxic conditions The metastatic process begins when tumour cells detach and migrate. These processes require a modification in cell–cell and cell–substrate interactions These interactions are under the control of several families of adhesion molecules, particularly the cadherins and integrins, and a number of proteolytic enzymes, such as the urokinase plasminogen activator (uPA). The aim of this study was to investigate the changes in expression of components of the metastatic cascade in human colon cancer cells when exposed to CO_2 and He pneumoperitoneums.
Methods: Human colonic cancer cell line SW1222 were exposed to an *in vitro* pneumoperitoneum of either air (control), CO_2 or He at 3 mmHg for 4 h at 37°C. Cells were then detached and incubated with primary antibodies against E-Cadherin, CD44, uPA receptor (uPAR) and β1 integrins, for 45 min at 4°C. Cells were washed three times and secondary FITC-anti-mouse IgG was added to cells for 30 min at 4°C. Cells were analysed for surface receptor expression by flow cytometry (FACScan, Becton Dickinson). Data obtained were confirmed by standard immunohistochemistry.
Results: The results are the mean fluorescent intensity expressed as a percentage of the control and standard error of the mean

	E-Cadherin	CD44	uPAR	β1
CO_2	44% ± 3*	80% ± 1*	200% ± 7*	80% ± 0 5*
He	68% ± 2*	90% ± 2†	135 ± *	85% ± 3*

†$P<0\ 05$ *versus* control, *$P<0\ 01$ *versus* control (Dunnett)

Conclusions: Exposure to a CO_2 and He pneumoperitoneum causes significant reduction in the expression of E-Cadherin, CD44 and β1 integrins, and a dramatic increase in the expression of uPA. All these receptors have pivotal roles within the process of metastasis and these changes will enhance metastatic potential, as a small change in expression has large functional significance which could provide a mechanism to explain how viable tumour cells detach from a primary and establish metastatic foci.

UGI 001

Evaluation of precision-cut human liver slices as a model to study hepatic cytokine production and metabolism

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Aims: Although purified human hepatocyte cultures have the advantage of providing information on a single liver cell population, they exclude the interaction between the different constituent cells in the liver (e.g. Kupffer cells) Culture of precision-cut human liver slices might provide a useful alternative model to elucidate the importance of such cell–cell interactions. Although this model has been used extensively for pharmacological studies, its applicability in studying human liver metabolism remains to be elucidated The aim is to evaluate precision-cut human liver slices as a model to study hepatic cytokine production and metabolism.
Methods: Using a Krumdieck tissue slicer, fresh liver slices (± 200 μm) were cut from wedge liver specimens from patients without an acute phase response undergoing resectional surgery for colorectal cancer metastases. The slices were placed in Netwell inserts in six well cell culture clusters. The tissue-culture clusters were placed in a humidified incubator at 37°C with 5 per cent CO_2 and air on a rocker platform. Slices were stimulated with 0 (controls), 0·1, 0·5 and 5·0 μg mL^{-1} LPS (endotoxin) and supernatants were assayed by ELISA for TNFα and IL-6 production
Results: The slices remained viable for 48 h as assessed by histomorphology and lactate dehydrogenase release A dose-dependent production of TNFα was observed at 8, 24, 48 h following endotoxin challenge A bell-shaped response was observed with IL-6 Preincubation with dexamethasone inhibited both TNFα and IL-6 production The table shows data at 24 h incubation.

Mean ± s d	Control	0·1 μg mL^{-1} LPS	0·5 μg mL^{-1} LPS	5·0 μg mL^{-1} LPS
IL-6 (ng mL^{-1})	0·07 ± 0·02	8·2 ± 0·9	14·2 ± 0·13	9·5 ± 0·43
TNFα (pg mL^{-1})	ND	10·0 ± 2·4	44·1 ± 10·6	70·4 ± 25·2

Conclusions: Human liver slices provide a model with which to study hepatic metabolism and in comparison with purified human hepatocyte cultures, may provide, useful information on the interaction between various cell populations in the hepatic environment

UGI 002

Assessment of hepatic steatosis using indocyanine green measurement by near-infrared spectroscopy

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Aims: Fatty livers are being used as a solution to donor organ shortage, there is no clinical technique which can assess the severity of fatty changes. Near-infrared spectroscopy (NIRS) can be used to measure directly hepatic indocyanine green (ICG) uptake and excretion rates. This study evaluated its application to assess the severity of fatty liver
Methods: New Zealand white rabbits (3·1 ± 0·6 kg) were used Fatty liver was induced by high-cholesterol diet (2 per cent) Four groups ($n=6$ per group) were used: group A (control); groups B, C and D were fed a high-cholesterol diet for 4, 8, and 12 weeks respectively Liver functions were measured Laparotomy was performed for liver exposure Hepatic artery (HABF), portal vein (PVBF) and total hepatic blood flow (THBF) were measured. Hepatic microcirculation (HM) was monitored Portal venous pressure (PVP) was measured via splenic vein cannulation ICG was given (0·5 mg kg^{-1}) intravenous. ICG concentration–time curve was generated and hepatic ICG uptake (α) and excretion rates (β) were calculated
Results: All cholesterol-fed animals showed macroscopic evidence of fatty changes, with evidence of portal hypertension in groups C and D In group B, there was no significant change in liver circulation, function and ICG uptake or excretion in comparison with controls With severe fatty changes (groups C and D), there was a significant reduction in PVBF and THBF with significant increase in HABF. HM also decreased and PVP increased in comparison with controls Groups C and D had significant alteration to liver function tests. In groups C and D, ICG uptake rate (α) and ICG excretion rate (β) were significantly reduced in comparison with controls ICG rate of uptake (α) significantly correlated with THBF ($r=0·94$, $P<0·001$) and HM ($r=0·96$, $P<0·001$), and albumin ($r=0·96$, $P<0·001$) ICG excretion rate (β) significantly correlates with bilirubin ($r=-0·89$, $P<0·001$), alanine aminotransferase ($r=-0·87$, $P<0·001$), aspartate aminotransferase ($r=-0·90$, $P<0·001$), and albumin ($r=0·95$, $P<0·001$)
Conclusions: In severe steatosis, ICG uptake rate measured directly by NIRS reflects reduced liver blood flow and microcirculation and its excretion rate correlates wit the degree of liver parenchymal dysfunction.

UGI 003

Major upper gastrointestinal surgery causes early systemic T-cell activation

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Aims: T-cell function has been considered dormant or suppressed following major surgery and of little relevance to the systemic inflammatory response syndrome (SIRS). This study questioned this thesis and studied T-cell activation in the early postoperative period.
Methods: Peripheral blood samples from eight patients undergoing major upper gastrointestinal surgery were examined before and at 24 h following surgery The expression of CD 25 (IL 2R), CD 62L (L-selectin) and CD 69 (T-cell activation marker) on CD 3 (pan-T-cell), CD4 (helper/inducer) and CD 8 (cytotoxic/suppresser) subpopulations of T-cells were studied using dual-labelled monoclonal antibodies and FACS analysis.
Results: There was no significant change in T-cell groups ratios following surgery ($P>0·15$) All T-cell subtypes showed significant activation following surgery. CD4+ and CD 8+ T-cells demonstrated significantly increased levels of CD 25 and CD 69 respectively (4142 *versus* 8471, 1779 *versus* 3646· events, $P<0·05$). The adhesion marker CD 62L expression was significantly decreased in the CD 3+ T-cell population postoperatively (3044 *versus* 1772. events, $P<0·05$), demonstrating global T-cell activation.
Conclusions: These findings confirm that surgery induces an early systemic activation of all T-cell subsets. This is counter to the thesis that major surgery is immunosuppressive and suggests that T-cell activation may have a role in the SIRS response after injury

UGI 004

Plasma levels of CXC chemokines ENA-78 and GRO-α are elevated in severe pancreatitis

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Aims: To investigate the systemic temporal profile of ELR motif positive CXC chemokines (ENA-78, GRO-α and IL-8), which have potent neutrophil chemoattractant and activating properties, in acute pancreatitis (AP) and relate this to disease severity.

Methods: Timed plasma samples from 44 patients admitted with AP were collected and stored at –80°C. Patients were divided into severe (23) and mild (21) according to the Atlanta criteria. Nineteen healthy donors were used to establish levels in a control population. ENA-78, GRO-α and IL-8 were measured using a sandwich ELISA technique.

Results: ENA-78 and GRO-α plasma levels were significantly higher in severe as compared with mild patients. ENA-78 results are shown in the table

Group	Admission	12 h	24 h	48 h
Severe	1231·5*	1750*	2339*	1848*
(n=23)	(197–3198)	(190–6674)	(166–10808)	(283–9759)
Mild	200·5	241	498·5	421
(n=21)	(0–1663)	(23–1839)	(9–2051)	(0–1916)

Results in pg mL^{-1}, median (range). *$P<0·001$, Mann–Whitney *U* test

Conclusions: Plasma levels of ENA-78 and GRO-α are elevated in severe AP and may contribute in part to systemic leukocyte activation and organ damage in this condition.

UGI 005

Use of human reliability assessment technique to evaluate the performance of animated laparoscopic cholecystectomy in training courses

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Aims: To evaluate the performance of laparoscopic cholecystectomy in training courses, using a modified human reliability assessment technique.

Methods: Endoscopic video records of 60 laparoscopic cholecystectomy performed by 60 surgeons during training courses were collected. A modified human reliability assessment approach was applied to evaluate task performance. The endpoints were the frequency of committed errors, error consequences and the external error modes to describe various ways in which the task may be erroneously performed.

Results: Analysis of 14 590 movements of endoscopic instruments identified 1071 errors and 335 intraoperative error complications. Some 168, 99, 32, eight and 11 errors with complications were committed by the hook, scissors, grasper, pledget and clip applicator in the course of 4421, 5883, 1964, 1989 and 333 movements respectively. The frequencies of damaging the liver bed, perforating the gall bladder and injury to the cystic artery or duct were 216, 73 and 20 respectively. The frequencies of error modes underlying complications were 187 for using too much force, 64 for inappropriate sequence of steps, 59 for missing steps, 13 for dissecting along wrong plane and six for incorrect instrument orientation.

Conclusions: Ergonomic assessment of surgical performance is a practical approach to evaluating the training process. The safest method of dissection was the pledget, while the hook led to the highest error rate. Errors with complications were either skill or rule based.

UGI 006

Loss of chromosome 9p is associated with intra-hepatic recurrence in hepatocellular carcinoma after curative resection

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Aims: Recurrence commonly occurs after curative resection of hepatocellular carcinoma (HCC). This study examined the genomic aberrations of HCC specimens from 31 patients who underwent curative resections of HCC using the technique of comparative genomic hybridization (CGH).

Methods: Tumour and normal reference DNA labelled with biotin-16-dUTP and digoxigenin-11-dUTP, respectively, by nick translation, were allowed to cohybridize competitively into normal metaphase chromosomes. After staining for the biotin and digoxigenin, and counterstaining, the hybridized metaphases were captured under fluorescence miroscopy. Digital image analysis by CGH software was then used to calculate the relative gains and losses of different chormosome regions. Clinical and pathological data of the 31 patients were prospectively collected.

Results: Seventeen patients developed intra-hepatic recurrence and 14 patients remained recurrence-free on a median follow-up of 25 months. There was no significant difference in the common aberrations (including 1q and 8q gain, 4q, 8p, 13q and 16q loss) between the recurrence-positive group and the recurrence-free group. However, loss of chromosome 9p was detected in seven patients in the recurrence-positive group (7/17, 41 per cent) while this was found in only one patient in the recurrence-free group (1/14, 7 per cent) (Fishers exact test, $P=0·045$). Loss of chromosome 9p remained significant in the prediction of recurrence by multivariate analysis ($P=0·046$). Other factors, including size and number of tumours, tumour differentiation, resection margin, encapsulation and presence of cirrhosis, were not significant in multivariate analysis. The disease-free survival of patients having loss of chromosome 9p was significantly shorter (log-ranked test, $P=0·036$).

Conclusions: Our current results therefore suggested that tumour suppressor genes residing on chromosome 9p such as *p16* may play a role in promoting HCC recurrence.

UGI 007

Does microvessel density provide prognostic information after potentially curative resection of gastric cancer?

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Aims: The aim of this study was to assess microvessel density (MVD) in gastric carcinomas after potentially curative resection and relate this to the development of disease recurrence.

Methods: Between July 1990 and May 1996, 79 patients underwent resection of a stage 1A, 1B or 2 gastric carcinoma. Five-micrometre sections from paraffin blocks were stained immunohistochemically with a monoclonal antibody JC70 [anti-CD31 Dako, UK] to highlight the microvessels. The slides were scanned at magnification ×40 and vascular hot spots identified. Ten separate fields were counted at ×400 magnification for each specimen, using the Chalkley grid method.

Results: There is no difference in MVD of stage 1B and 2 disease ($P=0·74$), but both these groups showed significantly increased MVD compared with stage 1A disease ($P=0·03$ and 0·006 respectively: Mann–Whitney)

Disease stage	No. patients	Recurrence	Mean vessel count ± s.e.m.
1A	23	2	48·09 ± 2·31
1B	21	5	53·33 ± 1·86
2	35	16	54·06 ± 2·04

For stage 1B or 2 disease, MVD was significantly greater in those developing recurrence ($n=21$) than those not ($n=35$): 57·62 *versus* 51·74 ($P=0·003$: Mann–Whitney). MVD was significantly higher in patients ($n=11$) with early recurrence (<18 months after surgery) than those developing recurrence later (>18 months): 60·23 *versus* 54·70 ($P=0·017$: Mann–Whitney)

Conclusions: Patients with stage 1B and 2 disease who develop recurrence have higher microvessel counts than those remaining well and this difference is greater in those developing early recurrence. Angiogenesis quantification by assessment of MVD can help to identify a subgroup of patients at risk of early recurrence but, despite the significant differences in mean MVD, there is considerable overlap between groups, suggesting that it is not likely to be useful for prognosis or selection for adjuvant therapy.

UGI 008

A neutralizing anti-CINC antibody reduces acute pancreatitis-associated lung injury

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Aims: The rat chemokine CINC is a potent neutrophil activator and chemoattractant; leukocytes play a critical role in acute pancreatitis (AP) and the development of distant organ damage This study examines the effect of blocking CINC activity on the development of AP and the associated lung injury.

Methods: AP was induced in adult Wistar rats by repeated intraperitoneal injections of caerulein ($50\,\mu g\,kg^{-1}\,h^{-1}$) Neutralizing anti-CINC antibody ($8\,mg\,kg^{-1}$ IP) was administered either prophylactically (before induction of AP) or therapeutically (following induction of AP). Severity of AP was determined by plasma amylase, pancreatic oedema and pancreatic myeloperoxidase activity (MPO) as a measure of neutrophil sequestration. Severity of pancreatitis-associated lung injury was determined by measuring pulmonary microvascular permeability (ratio of FITC-labelled albumin in lung lavage fluid to plasma) and lung MPO activity

Results: Pulmonary microvascular permeability was significantly reduced following prophylactic (0·42 ± 0·07 *versus* 0·78 ± 0·11) and therapeutic (0·31 ± 0·05 *versus* 0·79 ± 0·13) treatment with anti-CINC antibody ($P<0{\cdot}05$, $n=8$ in each group). Lung MPO activity was significantly reduced following prophylactic and therapeutic treatment with anti-CINC antibody ($P<0{\cdot}05$, $n=8$ in each group). Although there was no difference in severity of AP assessed by amylase and pancreatic oedema, neutrophil infiltration, determined by pancreatic MPO activity, was significantly reduced in rats following prophylactic and therapeutic treatment with anti-CINC antibody ($P<0{\cdot}05$, $n=8$ in each group).

Conclusions: Treatment with anti-CINC antibody results in significant protection against pancreatitis-associated lung injury and suggests that CINC plays a critical role in the inflammatory response associated with an attack of AP

UGI 009

Recombinant P-selectin glycoprotein ligand-Ig fusion protein (rPSGL-Ig) moderates neutrophil-mediated acid aspiration injury

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Aims: A central role for the polymorphonuclear leukocyte (PMN) in experimental acid aspiration has been demonstrated by the observation that PMN depletion reduced pulmonary vascular permeability Since neutrophil adhesion to the microvascular endothelium is thought to be a prerequisite in the sequence of events leading to PMN activation and injury, this study investigates the role of rPSGL-Ig, a P- and E-selectin antagonist, in moderating acid aspiration lung damage

Methods: Tracheostomy tubes were placed in male C57BL/6 mice and 0·1 N HCl was instilled into the trachea at $2\,mL\,kg^{-1}$ following intravenous injection of bovine I^{125} albumin. After 4 h the ratio of radiolabelled albumin in bronchoalveolar lavage (BAL) to blood was used to calculate the lung vascular permeability index (PI). An identical mouse preparation minus the administration of radiolabelled albumin was used to quantify neutrophils harvested from BAL fluid. PMN-depleted mice were compared with $1\,mg\,kg^{-1}$ rPSGL-Ig treated animals and $1\,mg\,kg^{-1}$ m20ek.Fc (negative control for rPSGL-Ig, which is inactive for selectin binding) treated group Additional sets of mice received rPSGL-Ig after acid aspiration but not before Animals were maintained in accordance with National Research Council guidelines.

Results: PI after subtraction of sham value (mean ± s.e., $P<0{\cdot}05$ by *t*-test with Bonferroni correction) in neutropenic mice ($n=15$) was 0·024 ± 0·003, a 63 per cent reduction compared with the untreated group, PI 0·064 ± 0·008 ($n=19$, $P<0{\cdot}05$). Similarly, PI of 0·026 ± 0·003 in mice treated with rPSGL-Ig represents 59 per cent protection ($n=17$, $P<0{\cdot}05$) PI of 0·063 ± 0·011 in m20ek.Fc-treated mice ($n=15$) was not significantly decreased. PMN count of 15 ± 5 in the BAL fluid in rPSGL-Ig-treated mice ($n=5$) was significantly less than the untreated group PMN count of 582 ± 72 ($n=5$, $P<0{\cdot}05$). There was no significant reduction in the BAL fluid PMN count of 552 ± 97 in m20ek.Fc-treated animals ($n=5$). PI in mice treated with rPSGL-Ig 0·5 h after acid aspiration ($n=14$) was 0·035 ± 0·003, a 45 per cent reduction from the untreated group ($P<0{\cdot}05$). Treatment with rPSGL-Ig 1 h following acid aspiration ($n=14$) reduced the PI to 0·039 ± 0·007, a 39 per cent protection ($P<0{\cdot}05$).

Conclusions: Endothelial selectin blockade is as effective as PMN depletion in attenuating acid aspiration-induced lung permeability In addition, delayed anti-selectin therapy following acid aspiration can decrease lung injury

Sepsis 001

Low molecular weight heparins induce osteoblast apoptosis – a putative mechanism for iatrogenic osteopenia?

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Aims: Low molecular weight heparins (LMWHs) are of undoubted efficacy as thromboprophylaxis in surgical practice We reported that LMWH therapy significantly delays fracture healing, while prolonged dosage inhibits bone nodule formation *in vitro* To investigate these phenomena further, we hypothesized that LMWHs would reduce osteoblast survival and, thus, bone formation by inducing programmed cell death (apoptosis)

Methods: Primary human osteoblasts were isolated from femoral heads excised during hip arthropasty and cultured to passage 3–5. These were grown to confluence and then incubated for 24 h in control medium or medium treated with enoxaparin ($200–2\times10^{-4}$ IU mL^{-1}) or combination of enoxaparin ($200–2\times10^{-4}$ IU mL^{-1}) and VEGF (1 ng mL^{-1}). Apoptosis was determined by measuring cytosolic histone-associated DNA fragmentation using an enzyme-linked immunosorbant assay. Results were confirmed by DNA fragmentation analysis on agarose gel electrophoresis. Cell functional viability was measured by a tetrazolium bioreduction colorimetric assay.

Results: Data are expressed as the percentage of control apoptosis or viability, illustrates mean ± s.e m and $n=4$ experiments in each case (see Table below)

Conclusions: Therapeutic doses of LMWH attenuate osteoblast survival by inducing significant apoptosis. This effect is partly abrogated by VEGF, which independently enhances osteoblast viability, thus delaying spontaneous and enoxaparin induced apoptosis. These findings may explain the bone resorptive effects of prolonged LMWH therapy and suggest a potential therapeutic role for VEGF in conditions of delayed bone formation

Control	200 IU mL^{-1}	20 IU mL^{-1}	2 IU mL^{-1}	0·2 IU mL^{-1}	0·02 IU mL^{-1}	0·002 IU mL^{-1}	0·0002 IU mL^{-1}
Effect of enoxaparin on osteoblast apoptosis							
100 ± 3	223 ± 8*	198 ± 7*	191 ± 6*	178 ± 2*	166·5 ± 1·5*	157 ± 8*	137 ± 7*
Effect of VEGF (1 ng mL^{-1}) on enoxaparin induced apoptosis							
51 ± 3#	218 ± 9#	197 ± 6#	164 ± 2#	141 ± 7#	118 ± 11#	96·4 ± 4#	85 ± 3#
Effect of enoxaparin on osteoblast viability							
100 ± 6	33 ± 5*	39 ± 2*	46 ± 9*	69 ± 7*	73 ± 4*	84·5 ± 8*	89·4 ± 2*
Effect of VEGF (1 ng mL^{-1}) on enoxaparin attenuated viability							
132 ± 7#	35 ± 4#	39 ± 5#	56 ± 3#	74 ± 7#	87 ± 1#	99 ± 3#	118 ± 6#

ANOVA was employed for statistical analysis, *versus control, #versus enoxaparin treated, $P<0·05$ was considered significant

Sepsis 002

Temporal changes in neutrophil (PMN) activation in intensive care unit (ICU) patients is dependent on diagnosis

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Aims: As PMNs are capable of causing tissue injury during inflammation, an assay of PMN respiratory burst activity may reflect the balance between systemic inflammatory (SIRS) and compensatory anti-inflammatory (CARS) response syndromes. It was hypothesized that such a balance would vary with time and disease process

Methods: Blood was taken from all patents admitted to a regional ICU on days 1, 3 and 7 following admission, as well as from age-matched controls. Diluted whole blood was stimulated with phorbol 1,2-myristate 1,3-acetate plus tumour necrosis factor alpha in the presence of luminol. The chemiluminesence resulting from the subsequent PMN respiratory burst was measured over 17·3 min using a BioOrbit 1251 Luminometer. The degree of PMN activation was calculated as the peak signal obtained divided by the white cell count ($\times10^{-7}$ mV per white cell).

Results:

	PMN respiratory burst activity ($\times10^{-7}$ mV per white cell)					
Diagnosis	Day 1		Day 3		Day 7	
Elective surgery	9·3 (6·8, 25·3)	[$n=5$]	–		–	
Emergency surgery/trauma	42·4 (4·5, 55·1)	[$n=7$][a]	61·0 (26·1, 94·4)*‡	[$n=10$]	25·3 (8·8, 32·4)	[$n=6$]
Nonoperative	19·4 (12·8, 48·5)	[$n=7$]	6·3 (4·1, 15·8)	[$n=3$]	29·4 (5·2, 53·6)	[$n=2$]
Neurosurgical	19·2 (10·3, 38·2)	[$n=15$]	29·8 (6·9, 79·1)	[$n=7$]	50·6 (49·2, 96·6)*†	[$n=3$]
Control	13·9 (11·0, 19·4)	[$n=24$]				

Analysis by Mann–Whitney U after ANOVA *$P\leq0·006$ *versus* control, †$P=0·021$ *versus* day 1, ‡$P=0·039$ *versus* day 7 [a]Data missing on three patients

Conclusions: Patients potentially at risk of multi-organ dysfunction exhibit temporal changes in PMN activation, the pattern of which depends on the underlying disease These results indicate that the inflammatory 'balance' of an injured patient may be determined by measuring PMN activation, identifying periods of susceptibility to a 'second hit' (excessive SIRS) or overwhelming infection (excessive CARS)

Sepsis 003

Adenosine attenuates acute lung injury in a model of endotoxaemia

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Aims: It was hypothesized that pulmonary dysfunction seen following endotoxin-induced acute lung injury in pigs would be attenuated by administration of adenosine, an endogenous anti-inflammatory agent

Methods: Fourteen random bred male pigs (27–34 kg) were anaesthetized with intravenous sodium pentobarbitone, intubated and ventilated They were randomized to receive an intravenous infusion of adenosine and Hartmann's solution (adenosine group) or Hartmann's solution alone (control) (adenosine 200 $\mu g\,kg^{-1}\,min^{-1}$ from induction of anaesthesia until $t=60$ min, then 100 $\mu g\,kg^{-1}\,min^{-1}$ until completion, Hartmann's solution at 1200 $mL\,h^{-1}$) All animals underwent a midline laparotomy. After 30 min stabilization ($t=0$), all animals received *E. coli* lipopolysaccharide (50 $\mu g\,kg^{-1}$) over 30 min. Fraction inspired O_2 (Fi O_2) and arterial blood gases were measured over 270 min At $t=240$, bronchoalveolar lavage (BAL) was carried out with 50 mL of Hartmann's solution. The experiment was terminated at $t=270$ min. Alveolar–arterial gradient was calculated using the formula $FiO_2\times710$ – (arterial $pCO_2/0·8$) – arterial pO_2 This is a measure of lung function with a large gradient indicative of impaired oxygen transport and, hence, lung injury

Results: One animal in the control group died 15 min following the BAL.

	A–a gradient (mmHg) (median (Q1, Q3))	
	$t=240$ min, pre-BAL	$t=270$ min, post-BAL
Control	472 85 (333 60, 527 75)	573 88 (558 13, 589 25)
Adenosine	172 15 (138 30 299 80)*	491 25 (289 38, 520 75)†

Adenosine *versus* time-matched control (Mann–Whitney *U* test) $^{*}P=0\ 026$, $^{\dagger}P=0\ 014$

Conclusions: Adenosine significantly attenuates the acute lung injury observed following a laparotomy and intravenous lipopolysaccharide in pigs This protective effect is also seen following the additional insult of BAL

Sepsis 004

Adenosine inhibits human neutrophil vascular endothelial growth factor (VEGF) release via A_2 receptor activation

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Aims: Activated human neutrophils (PMN) release vascular endothelial growth factor (VEGF) which may contribute to tumour growth as well as capillary leak syndrome during SIRS We investigated whether adenosine modulates VEGF release from activated PMN

Methods: PMNs were isolated from healthy adult volunteers and stimulated with tumour necrosis factor-α (TNF-α, 10 ng mL^{-1}) This was followed by incubation with adenosine and its receptor-specific analogues Culture supernatants were then assayed for VEGF using enzyme-linked immunosorbent assay

Results:

Per cent inhibition of control VEGF release from activated PMN

	1 μM	10 μM	100 μM
Ado	21 (8 1)*	35 5 (4 4)*	60 0 (3 8)*
Ado+DMPX (50 μM)	7 8 (3)	25 5 (4 6)	13 8 (2 8)*
A_2 Agonist (NECA)	37 2 (5 9)*	40 (4 4)*	50 (4 8)*

Data Mean (s d), $n=6$ Statistical analysis ANOVA, $^{*}P<0\ 05$

Adenosine (Ado) and its receptor-specific analogues dose-dependently inhibited the TNF-α-induced release of PMN VEGF. The relative order of IC_{35} values was adenosine (9 5 μM) > 5′-N-ethylcarboxamidoadenosine (NECA, 25 μM) > N^6-(3-iodobenzyl)-adenosine-5′-N-methyluronamide (44 μM) > N^6-cyclopentyladenosine (98 μM) This rank order of potency is consistent with the affinity order profile established for the human A_2 receptors The inhibitory effect of adenosine was reversed by the A_2 receptor antagonist 3,7-dimethyl-l-propargylxanthine (DMPX).

Conclusions: These data indicate that adenosine inhibits VEGF release from activated PMN via the A_2 receptor. This provides a novel target by which A_2 receptor-specific analogues may modulate VEGF-mediated proangiogenic responses and capillary leak syndrome.

Sepsis 005

Experimental study of induction of TNF-α production and mortality by bacterial lipoprotein: comparison with endotoxin/lipopolysaccharide

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Aims: Gram-negative bacteria can release both lipopolysaccharide (LPS) and bacterial lipoprotein (BLP), two major components in the outer membrane of bacteria It is well established that LPS plays a key role in the pathogenesis of sepsis/septic shock However, little is known about whether BLP is also independently responsible for the development of sepsis This study was carried out to investigate the effect of BLP on TNF-α production and animal survival in a murine model

Methods: Male MF-1 mice were randomized into three groups. BLP alone (IP, 15, 30, and 45 mg kg^{-1} body weight, $n=50$), LPS alone (IP, 15, 30, and 45 mg kg^{-1}, $n=50$), BLP plus LPS (IP, 15 and 30 mg kg^{-1}, $n=30$) Serum samples were collected at 30, 60, 90 and 120 min after BLP and LPS injection BLP- and LPS-induced mortality rates were recorded Serum TNF-α levels were measured by ELISA

Results:

Serum TNF-α levels (pg mL^{-1}) after LPS and BLP injection ($n=5$, mean ± s d)

	30 min	60 min	90 min	120 min
BLP	205 ± 43	774 ± 212	927 ± 234	399 ± 102
LPS	1176 ± 227*	3664 ± 1032*	4949 ± 819*	1784 ± 512*
LPS+BLP	1013 ± 172*	4912 ± 844*	5385 ± 346*	2615 ± 962*

Stats ANOVA, $^{*}P=0\ 05$ *versus* BLP

BLP at 15 and 30 mg kg^{-1} did not cause mortality, whereas LPS at 30 mg kg^{-1} resulted in a 10 per cent mortality rate at 24 h However, injection of mice with either BLP or LPS at 45 mg kg^{-1} induced 60 per cent and 80 per cent mortality rates in 24 h respectively. Moreover, the combination of BLP and LPS at a sublethal dose (30 mg kg^{-1}) caused a significant increase in mortality rate in mice (80 per cent vs 0 per cent and 10 per cent, $P<0\ 05$) Circulating TNF-α following BLP injection has a similar kinetic pattern to LPS-induced TNF-α production. However, BLP-induced circulating TNF-α levels at different time points were much less when compared with LPS-treated mice ($P<0\ 05$).

Conclusions: These results demonstrate that BLP released by bacteria is a potent inducer of sepsis/septic shock, and has a synergistic effect when combined with LPS. Low circulating TNF-α levels following BLP injection indicates that distinct mechanisms may be involved in BLP-induced sepsis/septic shock

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Sepsis 006

Pretreatment of the donor lungs with inhaled nitrous oxide modulates endothelial function and reduces neutrophil sequestration

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Aims: We have shown that donor pretreatment with inhaled nitrous oxide (NO) virtually abolishes acute lung injury (ALI) on a porcine single-lung transplant model. We sought to resolve whether this mechanism related to neutrophils or endothelium

Methods: A left-sided double-lumen tube was inserted through a tracheostomy incision in healthy female pigs weighing 50–55 kg after induction and general anaesthesia Cannulae were placed into the main pulmonary artery (PA) and left and right inferior pulmonary veins to obtain serial blood samples every 5 min for white cell and differential counts. NO at 20 ppm was delivered to one of the lungs for 20 min, after which 5 000 000 microspheres 3 μm in size were injected into the PA prior to flushing the lungs with cold modified Eurocollins solution. At the end of the flush, both lungs were then lavaged with 50 mL of normal saline for lymphocyte, neutrophil and microsphere counts and albumin estimation and biopsies were obtained to identify intercellular molecule-1 (ICAM-1) expression

Results: Before flushing, there was some sequestration of neutrophils in both lungs. There was more sequestration in the control lung even at 5 min ($P=0{\cdot}07$). Significant differences in the loss of white cells into lungs were noted at 10, 15 and 20 min of NO treatment ($P=0\ 029$, $P=0\ 017$ and $P=0\ 002$ respectively). There were more cells and protein in lavages of the control lung ($P=0{\cdot}001$ and $P=0{\cdot}021$) and microspheres were virtually absent in the treated lung ($P<0\ 001$). There was an impressive lack in the expression of ICAM-1 in the treated lungs.

Conclusions: Surgical trauma – sternotomy and cannulation – presumably causes endothelial activation as well as neutrophil activation and adherence within the lung, eventually leading to endothelial damage and leakage of cells into the alveoli, even in this nonbrainstem-dead model The striking reduction of sequestration and leakage seen with NO may explain some of its benefits in attenuating ALI

Sepsis 007

Bacterial lipoprotein induces tolerance in human THP-1 monocytes with reduced TNF-α production via a CD14-independent pathway

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Aims: Endotoxin tolerance is characterized by a diminished production of tumour necrosis factor-α (TNF-α) during prolonged exposure to lipopolysaccharide (LPS) and, therefore, represents an essential control mechanism during sepsis. However, it is unknown whether bacterial lipoprotein (BLP), another major component in bacterial wall, can cause tolerance. In this study we sought to determine if BLP pretreatment can induce tolerance in human THP-1 monocytes.
Methods: Human THP-1 monocytic cells were pretreated with culture medium alone and medium containing 10 ng mL^{-1} LPS or 10 ng mL^{-1} BLP for 24 h. Cells were further stimulated with high doses (100–1000 ng mL^{-1}) of LPS or BLP for 6 h Cells were washed and culture supernatants were collected and TNF-α levels were determined by ELISA. CD14 receptor expression on THP-1 monocytes was assessed by flow cytometry
Results:

TNF-α levels (pg mL^{-1}) after high doses of LPS and BLP stimulation ($n=4$, mean ± s d)

Pretreatment	0 1 μg mL^{-1} LPS	1 μg mL^{-1} LPS	0 1 μg mL^{-1} BLP	1 μg mL^{-1} BLP
Medium	501 ± 147	1318 ± 463	3041 ± 637*	2876 ± 644*
LPS	35 ± 5 0†	74 ± 28†	350 ± 86*†	239 ± 5 1*†
BLP	30 ± 7 5†	40 ± 9 5†	41 ± 9 0†	37 ± 6 7†

Stats ANOVA, *$P<0\ 05$ *versus* LPS stimulation, †$P<0\ 05$ *versus* medium pretreatment

When THP-1 cells were incubated with culture medium, BLP stimulation resulted in much higher TNF-α levels when compared with LPS stimulation ($P<0{\cdot}05$) Following LPS pretreatment, LPS stimulation-induced TNF-α production was significantly attenuated, whereas BLP stimulation still caused small amount of TNF-α. However, BLP pretreatment prevented both LPS and BLP stimulation-induced TNF-α production from THP-1 cells. FACScan analysis revealed that THP-1 monocytes do not express CD14 receptor
Conclusions: These results demonstrate that BLP has a more potent effect than LPS on THP-1 monocyte TNF-α production. Furthermore, BLP pretreatment is capable of inducing both endotoxin and bacterial lipoprotein tolerance via a CD14-independent pathway.

Sepsis 008

Local and remote organ injury following lower-torso ischemia–reperfusion is terminal complement component dependent

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Aims: Blockade of complement activation with soluble complement receptor type 1 (sCR1) which binds and degrades C3b and C4b has been shown to prevent local and remote organ injury following lower-torso ischaemia–reperfusion Utilizing C5-deficient mice, we now selectively examine the role of C5 and distal complement components in mediating local skeletal muscle and remote lung and liver injury following hind-limb ischaemia–reperfusion.
Methods: Two male congenic strains, C5-deficient (C5D; B10 D2/oSnJ) and wild-type (WT; B10·D2/nSnJ) mice were used in all experiments Bilateral tourniquets were placed above the greater trochanter of pentobarbital anaesthetized animals for 2 h After 3 h of reperfusion, the ratio of ^{125}I-albumin extravasation in the hind limb and in the bronchoalveolar lavage, to blood was used to calculate skeletal muscle and lung vascular permeability indices (PI) respectively. Liver injury was assessed by serum alanine aminotransferase (ALT, U L^{-1}) Polymorphonuclear neutrophil (PMN) sequestration was assayed by myeloperoxidase activity (MPO, U g^{-1}). C5D mice were compared with WT animals, WT mice treated with sCR1, and C5D animals reconstituted with WT serum. Animals were maintained in accordance with National Research Council guidelines
Results: Hind-limb PI after subtraction of sham value (mean ± s.e m., $P<0\ 05$ by t-test with Bonferroni correction) in C5D mice ($n=25$) was 1·07 ± 0·12, a 48 per cent reduction from WT PI=2 05 ± 0 10 ($n=29$) WT mice treated with 20 mg kg^{-1} sCR1 were similarly protected (PI=1 06 ± 0 06, $n=11$). C5D mice reconstituted with WT serum had 97 per cent of their injury restored (PI = 1·99 ± 0·16, $n=11$). Remote organ injury was equally moderated in C5D mice and sCR1-treated WT animals However, PMN sequestration in these organs was not significantly reduced, as indicated in the table (*$P<0\ 05$ compared with WT)

Groups	Lung PI (× 10^{-3})	Lung MPO	ALT	Liver MPO
C5D	0 3 ± 0 3*	60 ± 5	77 ± 6*	0 50 ± 0 10
WT + sCR1	0 3 ± 0 4*	45 ± 10	85 ± 10*	0 60 ± 0 10
C5D + WT serum	5 1 ± 1 1	Not assessed	127 ± 10	Not assessed
WT	4 9 ± 0 6	50 ± 5	132 ± 6	0 55 ± 0 05

Conclusions: Local skeletal muscle and remote lung and liver reperfusion injury is C5 and terminal complement component dependent. Remote organ neutrophil sequestration is complement independent

Sepsis 009

Single-lung transplantation with and without cardiopulmonary bypass

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Aims: Many transplant units avoid the use of cardiopulmonary bypass (CPB) for isolated lung transplants, owing to major concerns over aggravated lung reperfusion injury and excessive blood loss
Methods: We retrospectively reviewed our experience of single-lung transplantation to determine any adverse outcome. Some 115 single-lung transplants were undertaken between August 1986 and August 1998. We examined the postoperative oxygenation ratio at 1 and 24 h, and compared the extubation times of the two study groups. Mean blood loss and use of postoperative blood products and the rejection episodes were assessed Of these, 38 (33 per cent) were performed on bypass. The mean CPB time was 135 2 min. There were no differences in demographic data or primary pulmonary pathology between the groups.
Results: Donor organ ischaemic time was not significantly different in bypass (CPB) and nonbypass (NCPB) groups (256 7 min *versus* 241·9 min respectively, $P=0{\cdot}18$) Preoperative inspired oxygen/arterial oxygen content ratio (FiO$_2$/PaO$_2$) was not significantly different between NCPB and CPB single-lung transplant groups. At 1 h and 24 h postoperatively, the FiO$_2$/PaO$_2$ ratio was no different (mean 2 95 and 3·24 in NCPB cases; 3·53 and 3 75 in CPB patients, $P=0{\cdot}34$ and $P=0{\cdot}75$ respectively). Similarly, extubation times were not influenced by the use or otherwise of CPB Mean blood loss, however, was greater postoperatively in those cases performed on bypass (1254·2 mL *versus* 968 12 mL), although this was not statistically significant ($P=0\ 072$) Although the use of fresh frozen plasma (FFP) and platelets was similar in the two groups ($P=0{\cdot}64$ and

0·41 respectively), more blood was transfused during the postoperative care of patients undergoing single-lung transplantation performed on bypass ($P=0·02$). The number of acute rejection episodes proven by transbronchial biopsy in the first 30 days following transplantation was also no different.

Conclusions: Fears of poor lung graft function after operation involving cardiopulmonary bypass appear unfounded. We could detect no difference in function at 1 or 24 h, nor was there any difference in extubation time. The use of CPB appears to increase postoperative bleeding and the need for transfusion but CPB may be used safely to facilitate lung implantation.

Vascular 001

Macrophage elastase – a novel target for pharmacotherapy to prevent plaque disruption?

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Aims: Matrix metalloproteinases (MMPs) have been implicated in acute carotid plaque disruption which precedes cerebral thromboembolic symptoms. Macrophage elastase (MMP-12) is the most potent metallo-elastase described to date. The purpose of this study was to determine the presence of MMP-12 within carotid plaques and establish any association with plaque instability

Methods: Plaques were retrieved from 32 patients undergoing carotid endarterectomy, homogenized and MMP-12 quantified by immunoblotting using rabbit-antihuman MMP-12 antibodies. Products were identified corresponding to pro-MMP-12 (54 kD), an intermediate form (45 kD) and the 22 kD active enzyme.

Results: There was a significant increase in the level of active MMP-12 (22 kD) in symptomatic compared with asymptomatic plaques (arbitrary units, median (IQR))

	54 kD	45 kD	22 kD
Asymptomatic ($n = 14$)	5 3 (3 7–7 9)	5 1 (3 9–6 4)	1 6 (1 2–2 0)
Symptomatic ($n = 18$)	5 0 (3 4–6 4)	5 3 (3 8–6 1)	2 2 (1 6–2 8)
P	0 51	0 95	0 05

There was a significant increase in the level of both the active and intermediate forms of the enzyme in plaques with histological evidence of instability, particularly cap and shoulder foam cell infiltration, and for all forms compared with nondiseased artery Immunostaining confirmed that the enzyme was localized to macrophages.

Conclusions: The level of MMP-12 is significantly higher in symptomatic plaques. plus plaques with histological evidence of instability This enzyme may play a role in plaque destabilization and could represent a target for therapeutic inhibition

Vascular 002

Doxycycline penetrates the carotid plaque and inhibits MMP-9 secretion by macrophages *in vitro*

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Aims: Increased matrix metalloproteinase-9 (MMP-9) activity has been associated with instability of carotid plaques and its pharmacological inhibition is a potential target for carotid plaque stabilization The aims of this study were to determine whether doxycycline penetrates the carotid plaque *in vivo* and to determine whether it inhibits the expression of MMP-9 from monocyte-derived macrophages *in vitro*.

Methods: Some 100 consecutive carotid endarterectomy patients were randomized to either doxycycline 200 mg daily or placebo for a mean period of 6 weeks prior to carotid endarterectomy. Plasma and tissue concentrations of doxycycline were measured using high-performance liquid chromatography. Human monocytes derived from the peripheral blood were isolated and cultured in media conditioned with 0, 1, 10, and 100 mg mL^{-1} of doxycycline, in the presence or absence of 5 ng mL^{-1} of PMA. MMP activity in the culture medium was measured using quantitative gelatin zymography

Results: Mean plasma doxycycline concentrations varied between 2 2 and 5 2 µg mL^{-1}. Doxycycline concentrations in carotid plaques varied between 0 195 and 0 389 µg mL^{-1}. Pro MMMP-9 secretion by monocyte-derived macrophages in the absence of PMA stimulation is shown in the table. There was no significant difference between the PMA-stimulated and the non-PMA-stimulated groups at all levels of doxycycline concentration.

Doxycycline conc (mg mL^{-1})	0	1	10	100
Pro MMP-9,av optical density	1 5	1 5	1 3	0 5*
Active MMP-9,av optical density	0 7	0 7	0 4	0 08*

Conclusions: Doxycycline penetrates the carotid plaques at standard therapeutic doses It also inhibits the expression of MMP-9 by monocyte-derived macrophages in a dose-dependent manner *in vitro*, with potential implications for pharmacological carotid plaque stabilization

Vascular 003

Inhibition of Cox-1 reduces neointimal proliferation in an experimental model of carotid artery balloon injury

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Aims: Intimal hyperplasia, due to extensive vascular smooth muscle cell (VSMC) proliferation, remains a major cause of reocclusion after vascular intervention. Cyclo-oxygenase-1 (Cox-1) and cyclo-oxygense-2 (Cox-2) have recently been shown to be up-regulated in VSMCs in atheromatous plaque Therefore, we investigated the role of cyclo-oxygenase in initial hyperplasia postvascular injury

Methods: Thirty-one Sprague–Dawley rats were randomized into four groups. All groups underwent balloon injury to the left common carotid artery Intraoperatively and on alternate days postoperatively, Sc-58635 (specific Cox-2 inhibitor) was given to the Cox-2 group, Sc-560 (selective Cox-1 inhibitor) to the Cox-1 group and a combination of both inhibitors to the Cox-1 and -2 group Two weeks postoperatively carotid arteries were harvested and analysed for Cox-1 and Cox-2 using RT-PCR and immunohistochemistry Left carotid intima media area ratios (I/M ratio) were calculated using computerized planimetry

Results:

	Control	Cox-2	Cox-1	Cox-1 and -2
I/M ratio Mean ± s e m	1 73 ± 0 26	1 61 ± 0 17	1 03 ± 0 16*	1 05 ± 0 15*

ANOVA *$P < 0$ 05 *versus* control

Cox-2 was markedly up-regulated in the proliferating VSMCs of the neointima Cox-1 was also increased in these cells. While intimal hyperplasia was significantly reduced by Cox-1 inhibition and combined Cox-1 and Cox-2 inhibition, Cox-2 inhibition alone had no effect.

Conclusions: This study suggests that the up-regulation of Cox-2 in the VSMCs of the neointima is an epiphenomenon and paradoxically, its isoenzyme Cox-1 is involved in intimal hyperplasia Cox-1 inhibitors may have a therapeutic role in reducing intimal hyperplasia after vascular intervention.

Vascular 004

Effect of external stents on neointima formation in vein grafts implanted by end-to-side anastomosis

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Aims: Although oversized macroporous external stents have been shown to reduce neointima formation in porcine carotid artery–saphenous vein interposition grafts, it is not known whether stenting has a similar beneficial effect in an end-to-side model of saphenous vein bypass grafting, which is more analogous to arterial reconstructive surgery in man We therefore sought to develop a porcine model of end-to-side arteriovenous bypass grafting and compare morphologic changes in stented and contralateral unstented grafts in pigs 4 weeks after graft implantation.

Methods: In Large White pigs ($n = 6$) weighing 22–36 kg, segments of autologous long saphenous vein were implanted by end-to-side anastomoses into both common carotid arteries, bypassing surgically created occlusions One graft was externally supported with an oversized Dacron stent, the unstented contralateral graft acting as a control. After 4 weeks, the grafts were explanted and a representative number of transverse sections were subjected to morphometric analysis by computer-aided planimetry

Results: All grafts were patent at harvesting Both stented and control grafts had similar luminal diameters There was a significant reduction in both neointimal thickness and medial thickness in the stented graft compared with the unstented control grafts

	Control grafts	Stented grafts	P
Medial thickness (mm)	0 50 ± 0 07	0 3 ± 0 03	0 03
Intimal thickness (mm)	0 24 ± 0 02	0 13 ± 0 01	<0 001

Values expressed as mean ± s e m , $n = 6$ Statistical comparisons by paired t-test

Conclusions: This study demonstrates that external stenting reduces intimal and medial thickening in an end-to-side model of arteriovenous bypass grafting. This intervention has significant potential in reducing the incidence of late vein graft failure in coronary artery bypass grafting and infrainguinal bypass surgery

Vascular 005

Mechanisms of thrombogenicity in hyperhomocysteinaemia

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Aims: Hyperhomocysteinaemia is associated with increased arterial and venous thrombosis The mechanism of thrombogenicity has been the subject of controversy This study investigates, *in vitro*, the associations of elevated homocysteine with thrombosis.

Methods: (a) Thromboelastography (TEG), which allows global assessment of haemostatic function. was performed on fresh whole blood taken from nine healthy volunteers. Homocysteine was added to one portion to make a concentration of 50 μmol L^{-1}, and saline was added to a similar sample for use as a control. Reaction time (r), clot formation time (k), angle (α), maximum amplitude (MA) and clot lysis, were compared in both groups. Data are represented as mean (± s e m.) and Student's t-test was used for statistical analysis. (b) Platelet-rich plasma was also prepared from fresh blood samples in eight subjects Platelet shape change, a sensitive indicator of platelet activation, was measured in a channel analyser by changes in platelet volume. Homocysteine was added to the platelet-rich plasma to make final concentrations of 10 μmol L^{-1}, 20 μmol L^{-1}, 50 μmol L^{-1} and 100 μmol L^{-1}. The sample was incubated at 37°C for 15 min and platelet volume assessed at 0, 5, 10 and 15 min and compared to a saline control. Mann–Whitney U test was used for statistical analysis (c) Lactate dehydrogenase (LDH) is a predominantly red-cell enzyme, but leaks into the circulation after red-cell damage. In order to investigate whether the free sulfhydryl group of homocysteine damaged red-cell membranes and increased thrombogenicity, homocysteine was added to whole blood from 20 subjects to make concentrations of 0 μmol L^{-1}, 20 μmol L^{-1}, 50 μmol L^{-1} and 100 μmol L^{-1}, and incubated at 37°C for 15 min; serum was separated by centrifugation and LDH assay performed (Mann–Whitney U test).

Results: TEG analysis showed that the r time, which represents the rate of initial fibrin formation and is functionally related to plasma clotting factors and circulating inhibitor activity, was shorter with homocysteine, 34·39 (±1·72) *versus* 45·22 (± 2 87), ($P < 0{\cdot}0091$) Platelets shape change was not significantly different between homocysteine and controls over the concentrations and time points investigated. LDH levels were 358 (± 58), 369 (± 62), 368 (± 61) and 367 (± 57) for homocysteine concentrations of 0 μmol L^{-1}, 20 μmol L^{-1}, 50 μmol L^{-1} and 100 μmol L^{-1} respectively. There were no significant differences

Conclusions: Thrombosis in hyperhomocysteinaemia is not directly mediated by platelets. It appears that increased thrombogenicity occurs as a result of activation of plasma coagulation factors

Vascular 006

Diethylmaleate, a pro-oxidant, paradoxically attenuates ischaemia–reperfusion-induced lung injury

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Aims: Systemic ischaemia–reperfusion injury is an oxidant injury mediated by neutrophils Diethylmaleate, an intracellular pro-oxidant agent, has been shown to alleviate neutrophil-mediated tissue injury and the aim of this study was to evaluate whether diethylmaleate could have a protective effect on neutrophil-mediated lung injury in an animal model of lower-torso ischaemia–reperfusion.

Methods: Sprague–Dawley rats ($n = 7$/group) were randomized into three groups. the control group underwent midline laparotomy only; the ischaemic–reperfusion group (IR) underwent laparotomy and clamping of the infrarenal abdominal aorta for 30 min followed by 2 h of reperfusion, the third group (IR + DEM) was pretreated with diethylmaleate (6 mmol kg^{-1} intraperitoneally) 1 h before IR insult. Bronchoalveolar lavage protein concentration (BALprot) was used to measure microvascular leakage, while tissue myeloperoxidase activity (MPO) assessed pulmonary neutrophil infiltration

Results: Ischaemia–reperfusion resulted in a significant increase in both microvascular leakage and pulmonary neutrophil infiltration as measured by bronchoalveolar lavage protein concentration and pulmonary myeloperoxidase activity respectively Pretreatment with diethylmaleate significantly attenuated both microvascular leakage and neutrophil infiltration.

	Control	IR	IR+DEM
MPO (units g^{-1})	144 217 (9 85)	210 403 (10 56)	161 795 (5 62)*
BALprot (μg mL^{-1})	191 151 (22 82)	585 266 (96 00)	288 872 (47 53)†

Values are mean (s e m) *$P < 0$ 03 *versus* IR and IR–DEM, †$P = 0$ 07 *versus* IR and IR+DEM

Conclusions: Diethylmaleate preconditioning protects against ischaemia–reperfusion-induced lung injury. The protective effect of this pro-oxidant raises the possibility of using pro-oxidants to prevent inflammatory injury

Vascular 007

Treatment with rBPI$_{21}$ attenuates remote gut mucosal injury in lower-limb ischaemia–reperfusion injury

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Aims: Lower-limb ischaemia–reperfusion injury (IRI) is associated with increased gut permeability to endotoxin, which not only directly damages enterocytes but also stimulates a systemic inflammatory response syndrome (SIRS), compounding gut injury. Recombinant bactericidal/

permeability-increasing protein ($rBPI_{21}$, Xoma, USA) is a novel anti-endotoxin therapy with proven benefit in sepsis. We examined its potential role in modulating the remote gut injury in hind limb IRI.
Methods: Male Wistar rats prospective randomized control trial ($n=8$ per group). Control group and two groups undergoing 3 h bilateral hind limb ischaemia with 2 h reperfusion (I/R) were randomized to receive intravenous control protein Thaumatin at 2 mg kg^{-1} or rBPI at 2 mg kg^{-1} respectively We used quantitative morphometric assessment of the small bowel as a measure of gut injury and, using an *ex vivo* everted gut sac model, translocation of ^{14}C-labelled polyethylene glycol (PEG) as a measure of gut permeability
Results: Morphometric assessment of the small bowel showed a significant decrease in mean mucosal thickness in the I/R group, 0·47 ± 0·01 mm, compared with the control group, 0·58 ± 0·01 mm, and I/R rBPI-treated group, 0·61 ± 0·01 mm ($P<0{\cdot}001$). Villus height-to-crypt depth ratio was significantly decreased in the I/R group, 1·94 ± 0·05, compared to control, 2·82 ± 0·04, and I/R rBPI-treated group, 3·39 ± 0·1 ($P<0{\cdot}0001$) ^{14}C-labelled PEG translocation was significantly greater in the animals treated to ischaemia–reperfusion, 5·95 ± 2·8, compared to controls, 1·24 ± 0·29 ($P<0{\cdot}001$), and there was significantly less translocation in the I/R rBPI-treated group, 1·66 ± 0·79 ($P<0{\cdot}01$). Data represent mean ± standard error mean
Conclusions: These results indicate hind limb ischaemia–reperfusion injury is associated with a remote gut mucosal injury and increased permeability to macromolecules. Modulation in part by $rBPI_{21}$ anti-endotoxin therapy suggests endotoxin is harmful to the gut by direct effect or indirectly by stimulating systemic inflammation in this model

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Vascular 008

Pre-operative monocyte CD14 expression protects against organ dysfunction after visceral ischaemia and reperfusion

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Aims: We have previously shown correlation between intraoperative plasma endotoxin, neutrophil surface CD11b expression and postoperative organ dysfunction. This study investigates perioperative monocyte CD14 expression (the principal leukocyte endotoxin receptor), and the development of organ dysfunction
Methods: Arterial blood was collected prior to surgery, at 20-min intervals after visceral reperfusion, and at 24 and 48 h postoperation in 32 consecutive patients undergoing TAAA repair. Mean age, 65 years; 24 male, eight female, Crawford type, I 5, II 7, III 7 and IV 13. Surface expression of monocyte and neutrophil CD14 and CD11b was measured by flow cytometry Organ dysfunction was defined prospectively as failure of two or more organ systems. Daily multiple-organ dysfunction scores (MODS) and APACHE II scores were calculated.
Results: Two early deaths were excluded from analysis. Nine patients (30 per cent) developed postoperative dysfunction of two or more organ systems. In these patients the mean Day 1 MODS score was 12·3 (0·5) *versus* 10·0 (0·3) in patients who made an uneventful recovery ($P<0{\cdot}001$, Mann–Whitney) The organ failure group had significantly greater 24-h APACHE II scores (mean 23·1 (2·1) *versus* 14·1 (0·9), $P=0{\cdot}001$, Mann–Whitney). Six patients died The table shows perioperative monocyte CD14 surface expression in the two groups (*unpaired *t*-test)

	Pre-op	Clamp	1 h	4 h	8 h	24 h	48 h
Uneventful	76·5 (5·1)	58·8 (3·5)	59·3 (3·2)	71·1 (4·7)	84·7 (4·8)	72·2 (3·5)	73·1 (5·2)
Organ failure	59·0 (6·5)	57·8 (5·2)	55·0 (4·9)	65·1 (6·9)	60·6 (9·9)	67·5 (8·9)	64·8 (10·4)
P	0·05*	NS	NS	NS	0·02*	NS	NS

All data presented as mean (s.e.m.), NS, not significant ($P>0{\cdot}05$)

A significant difference in 60-min neutrophil CD11b was also observed (187 (32) *versus* 126 (10), $P=0{\cdot}033$*).
Conclusions: Preoperative monocyte CD14 phenotype predicted the risk of complications. Up-regulation of monocyte CD14 may be a protective response to endotoxin exposure after visceral ischaemia/reperfusion injury

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Vascular 009

Growth hormone prevents power-torso ischaemia–reperfusion-induced diaphragmatic dysfunction

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Aims: Previous work in our department has shown that lower-torso ischaemia–reperfusion injury (IR) induces significant diaphragmatic dysfunction 24 h following the initial injury This study assessed daphragmatic function following 2 h of lower-torso IR injury and the role of recombinant human growth hormone (rhGH) in attenuation of this injury
Methods: Male Sprague–Dawley rats ($n=18$) were randomized into three groups (a) control, (b) IR and (c) IR-treated with rhGH for 5 days preoperatively IR was achieved by placing an infrarenal aortic clamp for 30 min followed by 2 h of reperfusion. Diaphragm muscle contractile function was assessed *ex vivo* using electrical field stimulation in a tissue bath
Results: Results are expressed as peak tension and fatigability.

Group	Twitch (s.e.m.) (g)	Tetanus (s.e.m.) (g)	Fatigability (s.e.m.) (s)
Control	242·01 (38·45)	605·52 (77·63)	34·31 (4·6)
IR	108·55 (7·15)†	228·12 (14·38)†	19·5 (6·6)
IR + rhGH	319·14 (30·71)*	704·39 (45·69)*	30·1 (2·07)

*$P<0{\cdot}01$ *versus* IR, †$P<0{\cdot}05$ *versus* control Kruskal–Wallis ANOVA

Two hours of IR injury resulted in a significant impairment in diaphragmatic twitch and tetanic function compared with control. Pretreatment with rhGH significantly attenuated this injury.
Conclusions: This study demonstrated that IR produced a respiratory muscle mechanical dysfunction that was attenuated by pretreatment with rhGH This suggests that pretreatment with rhGH may have a role in clinical practice, particularly prior to elective vascular surgery

Patey Prize 009

Parathyroid hormone-related protein (PTHrP) and receptor expression in breast cancer and bone metastases

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Aims: PTHrP has been strongly linked to the development of bone metastases, and signals through a G protein coupled receptor (PTH-1R) The aim of this study was to determine the expression of PTHrP and PTH-1R in breast cancer and bone metastases, and to assess its correlation with other known prognostic markers of breast disease

Methods: PTH-1R mRNA expression was determined using gene-specific PCR and *in situ* hybridization of samples of normal breast, primary breast cancer and bone metastases. Expression of the PTH-1R was quantified with reference to a series of DNA abundance markers and normalized to the expression of GAPDH, ribosomal S29 and cytokeratin 18. Southern blotting with a radiolabelled oligonucleotide probe was performed to verify specificity and quantification of the PCR product Expression of 1-34 PTHrP ligand was determined using immunohistochemistry.

Results: Quantitative geometric mean PTH-1R expression was significantly higher in bone metastases when compared with breast tumours and normal breast ($P<0{\cdot}001$, ANOVA) In addition, a significantly higher number of bone metastases expressed the PTH-1R [19 of 23 (83 per cent)] when compared with all tumours [79 of 154 (51 per cent)] ($P<0{\cdot}01$, χ^2 test). No statistically significant correlations were found between PTH-1R receptor expression and other standard prognostic markers (tumour size, grade, nodal status and Ki67 antigen expression). Mortality from breast cancer at 5 years was significantly higher in PTH-1R-positive tumours (15/77 = 19 per cent) compared with PTH-1R-negative tumours (6/77 = 8 per cent) ($P<0{\cdot}05$, χ^2 test). Additionally, 36 per cent of tumours coexpressed ligand and receptor and 5-year survival in this group was the poorest (33 per cent *versus* 7 per cent, $P<0{\cdot}01$).

Conclusions: The significantly higher expression of PTHrP receptor in bone metastases supports a role for the receptor in their development. In addition, primary breast cancers coexpressing ligand and receptor have a worse clinical prognosis

Patey Prize 010

Tumour-induced apoptosis: a novel mechanism of peritoneal invasion

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Aims: The mechanisms by which tumour cells invade peritoneal surfaces are unclear The aim of these studies was to investigate the potential role of apoptosis in peritoneal invasion.

Methods: Mesothelial cultures were prepared from omental biopsies, grown to confluence on glass coverslips and seeded with SW480 colonic tumour cells at an effector:receptor ratio of 0·5:1 Phase-contrast microscopy and Tdt-mediated dUTP nick-end labelling (TUNEL) staining were used to determine tumour-induced mesothelial apoptosis. Potential death ligands and their receptors were investigated in SW480 and mesothelial cells by both RT-PCR and immunofluorescence microscopy. Tumour-induced apoptosis was quantified in TUNEL-stained samples by determining the apoptotic index of five random high power (×200) fields using image analysis software and repeated in triplicate. The contribution of FasL/Fas to mesothelial apoptosis was determined by the addition of SW480 cells, preincubated with a competing FasL monoclonal antibody (anti-FasL), to the coculture model. Ligand and receptor interaction was studied by confocal microscopy.

Results: Coculture of SW480 with mesothelial monolayers produced morphological changes consistent with apoptosis, which was confirmed by TUNEL staining. Median apoptotic indices (interquartile range) were as follows.

	Without anti-FasL	With anti-FasL
Mesothelial cells alone	**2 (0–4)**	0 (0–2)
Tumour cells alone	0 (0–0)	0 (0–0)
Cocultures	**8 (8–14)**	2 (2–4)

A significant increase in mesothelial apoptosis was observed in cocultures as compared with monolayers alone ($P<0{\cdot}0001$, Mann–Whitney U test), which was reduced by treatment with competing anti-FasL antibody ($P<0{\cdot}0001$, Mann–Whitney U test). Both SW480 and mesothelial cells expressed FasL and Fas at the mRNA and protein level Confocal microscopy colocalized tumour FasL and mesothelial Fas expression to areas of tumour–mesothelial cell interaction

Conclusions: Tumour cells induce mesothelial killing via an apoptotic mechanism involving Fas/FasL. This novel mechanism of mesothelial invasion represents a potential target for the prevention of peritoneal tumour metastasis

Patey Prize 011

Granulocyte-macrophage colony stimulating factor (GM-CSF) upregulates neutrophil vascular endothelial growth factor (VEGF) release: a potential factor in the development of systemic inflammatory response syndrome (SIRS)

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Aims: VEGF and GM-CSF levels are markedly elevated in SIRS The raised GM-CSF levels delay neutrophil (PMN) apoptosis. We investigated the effects of (1) GM-CSF on PMN VEGF release and (2) VEGF on PMN activation and transendothelial migration (TEM)

Methods: PMNs were isolated from healthy volunteers ($n=5$) and stimulated with tumour necrosis factor-α (TNF-α, 10 ng mL^{-1}). *Experiment 1*: unstimulated and stimulated PMN were treated with recombinant human GM-CSF (rhGM-CSF) at various doses and VEGF release was assessed using enzyme-linked immunosorbent assay. *Experiment 2*: PMN TEM across a human umbilical vein endothelial cell (HUVEC) monolayer which had been pretreated with recombinant VEGF (rhVEGF) was assessed. In a separate group, PMN were prestimulated with VEGF and then added to unstimulated HUVEC monolayer. *Experiment 3* PMN adhesion receptor molecule (CD11a/b, CD18) expression following pretreatment with VEGF was assessed using flow cytometry

Results:

	Control	rhGM-CSF 1 ng	rhGM-CSF 5 ng	rhGM-CSF 10 ng
2 h VEGF	25·5 ± 5·4*	101·7 ± 40·8*	79·6 ± 22·6*	77·3 ± 26·1*
6 h VEGF	22·3 ± 7·1*	41·7 ± 10·0*	46·5 ± 14·3*	30·5 ± 7·3

Data mean ± s.e.m., paired t test (*$P<0{\cdot}05$), VEGF levels (pg mL^{-1})

Compared with controls, VEGF release was significantly increased by stimulation with TNF-α (18·5 ± 5·6 *versus* 170·5 ± 45·6, $P<0{\cdot}05$) with no further up-regulation by GM-CSF (18·5 ± 5·6 *versus* 168·2 ± 39·7, $P<0{\cdot}05$), suggesting a saturable response. PMN pretreatment with rhVEGF resulted in no significant difference in TEM compared with the control. In contrast, rhVEGF pretreatment of HUVEC monolayer significantly enhanced PMN TEM compared with the control. PMN adhesion receptor expression was unaffected by rhVEGF pretreatment.

Conclusions: This study demonstrates that GM-CSF up-regulates PMN VEGF release, while VEGF induces PMN TEM through an endothelial cell-dependent mechanism. Thus, elevated GM-CSF may perpetuate SIRS through a VEGF-dependent mechanism

Patey Prize 012

Effect of external biodegradable stents on graft wall thickening in experimental vein grafts

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Aims: External, nonrestrictive, macroporous stents prevent neointima formation in porcine vein grafts and have been proposed as a therapeutic approach to the prevention of late vein graft failure. Since these stents are nonbiodegradable and, therefore, may elicit deleterious long-term, inflammatory, infective and mechanical complications, the effect of external macroporous biodegradable (polyglactin) stents on neointimal and medial thickening in porcine vein grafts was investigated.
Methods: Bilateral vein saphenous vein–carotid artery interposition grafting was performed in Large White pigs (22–36 kg, $n=4$) with external placement of 8-mm diameter polyglactin stents on one side, the contralateral side acting as a control. One month after surgery, graft wall dimensions were measured on histological sections using computer-aided planimetry.
Results: Polyglactin stents significantly reduced medial thickening compared with the control (unstented) grafts. No statistically significant reduction in neointimal thickening was found.

	Control grafts	Stented grafts	*P* value
Medial thickness (mm)	0.42 ± 0.04	0.24 ± 0.03	0.02
Intimal thickness (mm	0.15 ± 0.01	0.12 ± 0.01	NS

Values expressed as mean ± s.e.m., $n=4$. Statistical comparisons by paired *t*-test

Conclusions: An oversize biodegradable stent reduces medial thickening, a component of late vein graft failure in experimental grafts. If subsequent studies confirm preservation of this beneficial effect once the stent biodegrades, this form of stent may have an advantage over permanent stent material with potential for clinical application.

Patey Prize 013

Pravastatin attenuates the microvascular response to injury in a diabetic model

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Aims: Diabetes mellitus exacerbates the microvascular response to injury. Pravastatin, a HMG Co A reductase inhibitor, is known to have endothelial protective effects independent of its lipid-lowering ability. Therefore, we hypothesized that Pravastatin would attenuate the microvascular response to injury in an experimental model of diabetes mellitus.
Methods: Subjecting the mesenteric circulation to a short ischaemia–reperfusion (I-R) injury induces microvascular injury. Sprague–Dawley rats ($n=18$) were randomized into three groups: (a) control, (b) diabetic, (c) diabetic treated with Pravastatin. A mesenteric venule was examined pre- and post-I-R using intravital microscopy. Leucocyte rolling velocity, a P-selectin-mediated response and leucocyte adhesion and migration, an ICAM-1 and CD-11/CD-18 dependent response, were then measured.
Results:
Expressed as mean (s.e.m.), following 60 min reperfusion.

Group	Rolling velocity ($\mu m\ s^{-1}$)	Adherence (cells per field)	Migration (cells per field)
Control	30.48 (3.48)	11.3 (0.8)	4.5 (0.5)
Diabetic	16.63 (1.76)†	19.2 (1.3)†	7.71 (0.9)†
Pravastatin	41.68 (6.5)*	6.8 (0.8)*	2.67 (0.7)*

*$P<0.01$ *versus* diabetic, $P<0.05$ *versus* control ANOVA, Tukey–Kramer *post hoc* test

These data demonstrate a significant increase in leucocyte rolling velocity and decrease in leucocyte adherence and migration in the treated diabetic group compared with those untreated.
Conclusions: We have shown that Pravastatin in an experimental model of diabetes mellitus significantly attenuates microvascular response to injury and protects endothelial integrity following I-R. This study demonstrates that Pravastatin has microvascular protective effects which may benefit the diabetic patient at risk of cardiovascular disease.

Patey Prize 014

Prediction of early post-transplant function of nonheartbeating donor lungs

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Aims: Nonheartbeating donors' (NHBD) lungs are a promising supply of extra organs for transplantation. We aimed to develop an isolated ventilation and perfusion technique to assess the degree of warm ischaemic organ injury suffered prior to retrieval.
Methods: All animals were anaesthetized throughout and euthanazed without regaining consciousness. Lungs from Landrace cross pigs (approx. 50 kg) were retrieved after 1 h (NHBD1) or 2 h (NHBD2) post-hypoxic death. Control organs were retrieved using standard techniques from matched animals immediately after aortic cross-clamping. Modified Eurocollins pulmoplegia was used, prior to ventilating a single lung from each animal with 100 per cent oxygen and perfusion for 6 min with deoxygenated and neutrophil-depleted blood. For the NHBD2 group, the contralateral lung was transplanted with post-transplant function assessed.
Results: On assessment, oxygenation at 6 min did not differ between NHBD1 ($n=4$), mean 57 (s.d. = 16) kPa *versus* controls ($n=5$), 61 (5), but deteriorated significantly in NHBD2 ($n=6$), 45 (15) *versus* controls ($n=8$), 62 (3), $P<0.05$. Pulmonary vascular resistances did not differ significantly between groups, NHBD1, 29 (9) Wood units *versus* controls, 30 (5); NHBD2, 52 (29) *versus* controls, 34 (19), after 6 min. NHBD2 transplanted contralateral lungs showed a significant deterioration in oxygenation after 5 h ($n=6$), 32 (20) kPa, *versus* matched controls ($n=6$), 67 (14).
Conclusions: The assessment technique shows significant deterioration in oxygenating performance after 2 h warm ischaemia, but no deterioration after 1 h. A similar deterioration in oxygenating capacity was observed post-lung transplantation, suggesting this method may detect occult warm ischaemic damage.

Patey Prize 015

Bacterial lipoprotein (BLP) delays neutrophil apoptosis – a putative mediator of SIRS?

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Aims: Lipopolysaccharide (LPS) is considered the most potent exogenous mediator of the systemic inflammatory response syndrome (SIRS) which results, in part, from delayed neutrophil (PMN) apoptosis. The effects of another ubiquitous bacterial component, bacterial lipoprotein (BLP), the most abundant protein in the cell wall of all bacteria, on PMN apoptosis are unknown. We investigated the potential role of BLP in the regulation of PMN apoptosis and compared these effects with those of LPS.
Methods: PMNs from healthy volunteers were isolated and exposed to identical concentrations of LPS and BLP. PMN apoptosis was assessed six hourly using Annexin V/propidium iodide staining and confirmed on cell morphology. PMN activation was assessed flow cytometrically using CD11b and CD18 receptor expression as functional markers

Results: Per cent PMN apoptosis (mean ± s.d.). Statistical analysis: ANOVA (*$P < 0·0005$)

Time (h)	Control	BLP 10 µg	BLP 100 µg	BLP 1000 µg	LPS 10 µg	LPS 100 µg	LPS 1000 µg
6	11·2 ± 4·4	7·7 ± 2·7	6·9 ± 4·6*	6·5 ± 3·4*	6·9 ± 2·9*	6 ± 3·5*	7·1 ± 2*
12	23·6 ± 11·8	12 ± 3·7*	10 ± 4·2*	8 ± 3·4*	8·8 ± 2·9*	8 ± 3·1*	9 ± 3·9*
18	41·3 ± 7·2	26 ± 6·3*	17 ± 4·5*	18 ± 4·7*	15 ± 5·2*	16 ± 4*	15 ± 5·7*
24	52·6 ± 5·5	36 ± 6·3*	31 ± 5*	31 ± 7·5*	27 ± 11*	27 ± 8*	28 ± 8·8*

BLP significantly delayed PMN apoptosis and up-regulated PMN adhesion receptor expression compared with control values. The effects seen were markedly similar to LPS

Conclusions: Our data demonstrate for the first time that BLP, present in all bacterial pathogens, is capable of up-regulating PMN adhesion receptor expression and delaying PMN apoptosis in a time- and dose-dependent manner. The potency of, and the effects mediated by BLP are very similar to those of LPS. This identifies BLP as a putative mediator of SIRS and demands that due attention be paid to other bacterial products in the investigation and treatment of septic states.

Patey Prize 016

Serum VEGF and VCAM: Value as markers of angiogensis and metastasis in breast cancer

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Aims: Production of the potent endothelial mitogen vascular endothelial growth factor (VEGF) correlates, in breast cancer cytosols, with the developmet of angiogenesis (assessed by microvessel density) and induces vascular cell adhesion molecule (VCAM) expression in endothelial cells and both have soluble isoforms detectable in serum The aim of this study was to assess the value of serum VCAM and VEGF in predicting tumour angiogenesis and metastasis

Methods: Serum levels of soluble VCAM and VEGF were measured in women with early breast cancer (EBC) ($n = 147$) and women with progressing advanced breast cancer (ABC) ($n = 36$) using ELISA (R&D Systems Ltd., Oxon, UK) Serum measurements were compared with known histological prognostic parameters and with microvessel density (MVD) by immunostaining tumours with the CD31 antigen Statistics by log T test and Pearson correlation

Results: In EBC serum levels of VCAM (mean 743·5 ng mL^{-1}, range 263–1421) were higher than in both pre- and postmenopausal controls (483 ng mL^{-1} and 478 ng mL^{-1}, $P < 0·001$ and $P = 0·01$ respectively) Levels of serum VEGF in EBC (mean 299 pg mL^{-1}, range 47·1–1321) were raised only when compared with premenopausal women (104 pg mL^{-1}, range 30·5–129·9, $P < 0·01$) Levels of serum VCAM, but not VEGF, correlated with MVD ($r = 0·67$, $P < 0·001$). Serum VCAM, but not VEGF, was raised in women with ABC (mean 1236, range 349–3914) when compared with EBC ($P < 0·001$) and normal controls

Conclusions: Serum VCAM is a sensitive marker of angiogenesis in breast cancer that could be used to assess responses to therapy in women with ABC and may have prognostic value in EBC. Measurement of serum VEGF does not provide diagnostic or prognostically valuable information

Colorectal 001

Antioxidant N-acetylcysteine modulates 5-fluorouracil activity against colorectal cancer xenografts an experimental model

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Aims: The antioxidant pyrrolidinedithiocarbamate (PDTC) promotes cytotoxicity of 5-FU against human colorectal cancer (CRC) xenografts. We investigated the effects of a second antioxidant N-acetylcysteine (NAC) on human CRC xenograft growth in the nude mouse. NAC is of interest as it is licensed for clinical use in high doses to treat paracetamol poisoning.

Methods: Athymic nude mice ($n = 28$) were injected subcutaneously in each flank with the mutant p53 human CRC cell line, HCT15 (1×10^6 cells at each site). Treatment was administered by intraperitoneal injection when tumours were visible at day 7 Groups included: (1) saline 0·2 mL, (2) 5-FU 120 mg kg^{-1}, (3) NAC 200 mg kg^{-1}, (4) NAC and 5-FU. Serial measurements of tumour volume were made in a blinded fashion. Mice were culled when individual tumour volume exceeded 1000 mm^3.

Results: Prior to treatment at day 7, there was no significant difference between groups ($P = 0·18$, Kruskal–Wallis). NAC administered as a single agent does not retard tumour growth ($P = 0·31$, Mann–Whitney) Tumour volume is significantly reduced from day 13 in mice treated with NAC/5-FU compared with those treated with 5-FU alone (day 13, $P = 0·03$, days 17 and 20, $P < 0·001$, Mann–Whitney).

Treatment (*n*)	Combined tumour volume per animal (mm^3) (mean±s d)				
	Day 7	Day 10	Day 13	Day 17	Day 20
Control (5)	379 ± 81	1864 ± 462	–	–	–
5-FU (9)	217 ± 125	311 ± 149	522 ± 247	1227 ± 681	2403 ± 985
NAC/5-FU (9)	256 ± 92	209 ± 88	304 ± 154	334 ± 190	510 ± 252

Conclusions: Growth of established human CRC xenografts was retarded more effectively by combined therapy with NAC/5-FU than by 5-FU alone. The mode of action of antioxidants as adjuncts to established chemotherapy remains to be determined.

Colorectal 002

Anti-vascular endothelial growth factor attenuates post-operative peritoneal adhesion formation without adversely affecting wound or anastomotic integrity

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Aims: Postoperative intra-abdominal adhesion formation remains a significant cause of complications in surgical patients To date, no agent has been shown to block consistently adhesion formation, preliminary evidence has shown that intra-abdominal adhesion formation is angiogenesis-dependent Vascular endothelial growth factor (VEGF) is a potent stimulator of angiogenesis and promotes vascular leakage. We determined whether a specific VEGF monoclonal antibody (mAb) could prevent postoperative adhesion formation without affecting wound and anastomotic integrity.

Methods: After developing a standardized peritoneal injury which resulted in a reproducible adhesion model, 40 CD-1 mice were randomized and treated intraperitoneally with either VEGF mAb ($n = 20$) or IgG isotype control mAb ($n = 20$) at the time of abdominal closure. Animals ($n = 10$ per group) were sacrificed on postoperative day 14, and the development of intra-abdominal adhesions was determined and graded blindly using well-established criteria. Animals ($n = 10$ per group) were also sacrificed 10 days postoperatively and their laparotomy wound and gastrointestinal anastomoses were assessed by tensiometry Statistical analyses were performed using the Mann–Whitney and Fisher's exact tests.

Results:

Adhesion scores and wound breaking strength (N)

	Adhesion score					
Grade	0	1	2	3	Laparotomy wound	Gastrointestinal anastomosis
VEGF mAb	8	1	1	0	0·89 ± 0·18	0·68 ± 0·12
IgG mAb	0	1	3	6	0·92 ± 0·25	0·71 ± 0·14

Treatment with VEGF mAb resulted in a significantly lower incidence of adhesion formation compared with control animals ($P < 0·001$). Furthermore, intergroup analysis for the presence of marked adhesions (grade 2 or 3) demonstrated that mice treated with VEGF mAb had a significantly lower incidence of advanced adhesions when compared with controls (10 per cent *versus* 90 per cent). Laparotomy wound and gastrointestinal anastomotic strength were similar between groups

Conclusions: This study demonstrates that the formation of postoperative intra-abdominal adhesions is attenuated following the administration of VEGF mAb without adversely affecting wound strength or anastomotic integrity

Colorectal 003

CT colonography: still at the development stage?

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Aims: Recent reports have suggested that CT colonography (virtual colonoscopy) may be as sensitive as colonoscopy in investigating patients at high risk from colorectal neoplasia. We have been conducting a prospective trial to establish the sensitivity and specificity of CT colonography in the investigation of patients over 55 years old with rectal bleeding.

Methods: CT colonography was performed in 25 patients (median age 71, interquartile range 57–77) immediately before conventional colonoscopy Any patient with recent large bowel investigations or a history of colorectal neoplasia were excluded CT colonography was performed using a standard protocol by a radiologist who had previous experience of 50 examinations in patients with known polyps or cancer. The endoscopists were blind to the findings on CT.

Results: A colonoscopy to caecum was performed in 24 (96 per cent) of the patients A polyp 1 cm or more in size, or carcinoma was found in six (five polyps, one carcinoma, size range, 10–55 mm) Only one of these lesions was identified by CT colonography. False positives were reported in four patients (eight lesions; size range, 6–44 mm) with two being reported as strongly suspicious for carcinoma. These results give a per-patient sensitivity of 17 per cent and specificity of 84 per cent. This poor outcome would appear to be related to the high incidence of severe diverticular disease (52 per cent) in an elderly population

Conclusions: While there is a great deal of enthusiasm for this new technique, our results demonstrate that CT colonography is still at the developmental stage and requires significant modification before it can be recommended for the investigation of patients with large bowel symptoms.

Colorectal 004

Tissue factor expression and angiogenesis in colorectal carcinoma

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Aims: Tissue factor is the main initiator of coagulation but, recently, it has been suggested that it may be involved in tumour angiogenesis. The aim of this study was to assess tissue factor expression in human colorectal carcinomas and compare it with microvessel density.

Methods: Samples were taken from fresh colorectal carcinoma specimens and background mucosa and stored at –80°C. Biopsies were taken from patients undergoing colonoscopy in whom this was normal to act as controls Tissue factor (TF) levels in tumour, background mucosa and control specimen homogenates were measured using an enzyme-linked immunosorbent assay Histological sections of the tumours were stained using the monoclonal antibody JC70 (anti-CD31) and microvessels counted in vascular hot spots in 10 fields per specimen using the Chalkley grid method

Results: TF levels were significantly elevated in colorectal carcinomas compared with normal controls and background mucosa ($P=0\ 003$ and $P=0\ 0012$, Mann–Whitney)

Specimen	Number	Mean TF concentration (ng mg^{-1})
Normal controls	20	20 70 ± 1 66
Background mucosa	53	20 17 ± 2 01
Colorectal carcinoma	53	26 11 ± 2 45

The mean cumulative microvessel count for the tumours was 51 32 Tumours were separated into a hypervascular group ($n=25$) having a vessel count of 52 or greater, and a hypovascular group ($n=28$) having a count of 51 or less. Mean TF concentration (ng mg^{-1}) was significantly higher in the hypervascular group compared with the hypovascular group· 29 24 *versus* 23 32 ($P=0\ 008$, Mann–Whitney).

Conclusions: TF levels are increased in colorectal carcinomas compared with background mucosa and normal controls Mean TF concentration is significantly higher in tumours with increased microvessel density, indicating that it may play a role in tumour angiogenesis

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Colorectal 005

Correlation of plasma and serum vascular endothelial growth factor (VEGF) with platelet count in colorectal cancer (CRC): clinical evidence of platelet scavenging

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Aims: VEGF is important in tumour angiogenesis, but platelet activation and release of VEGF have meant that there is uncertainty as to whether plasma or serum should be used to measure circulating VEGF This study has compared serum and plasma VEGF with platelet counts in colorectal cancer both before and after surgical resection.

Methods: Serum and plasma samples were collected from 166 primary CRC patients and 116 control patients, 90 patients underwent CRC resection and 32 patients colorectal resection for benign disease Postoperative samples were taken 4–6 h and 14–20 h after surgery

Results: Plasma VEGF and serum VEGF were significantly higher in CRC patients (18 5 pg mL^{-1} and 327 pg mL^{-1}) compared with control patients (9 0 pg mL^{-1} and 151·5 pg mL^{-1} respectively) ($P<0\ 0001$). Paired serum and plasma VEGF measurements correlated in both CRC patients ($r=0\ 56$) and patients with benign disease ($r=0\ 73$) ($P<0\ 0001$) Serum and plasma VEGF levels correlated with platelet count in CRC patients ($r=0\ 58$ and $r=0\ 44$ respectively), but did not do so in control patients. Plasma and serum VEGF increased with advancing stage of disease. The amount of VEGF per platelet increased with stage, suggesting platelet uptake The correlation of serum and plasma VEGF with platelets in CRC but not in benign disease may be a result of scavenging of VEGF from the tumour source by platelets, with plasma levels reflecting free-circulating VEGF after platelet saturation

Conclusions: Plasma VEGF is detectable but values are low and lie at the lower end of the ELISA's sensitivity. At present, it is not known whether serum or plasma VEGF levels are clinically most informative and, hence, both should be measured, with the platelet count to measure VEGF/platelet, in studies correlating VEGF with prognosis

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Colorectal 006

Detection of peripheral blood micrometastastases in colorectal cancer

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Aims: To identify patients at risk from treatment failure after curative surgery for colorectal cancer (CRC) using the polymerase chain reaction (PCR) to detect micrometastases during follow-up

Methods: We have developed a one-tube, robust, highly reproducible and specific protocol using fully quantitative RT-PCR based on the 5′-nuclease assay An automated detector records fluorescence derived from probes binding to amplified DNA and generates a PCR cycle number, the threshold cycle, Ct This value is the first cycle at which the system detects fluorescence above the baseline level By constructing standard curves for each marker using known numbers of mRNA molecules, Ct values can be translated into quantitative mRNA copy numbers.

Results: Detection of cytokeratin 20 (CK20) has been linked with the presence of micrometastases in peripheral blood (PB). We show that its mRNA is detected in 100 per cent of PB samples taken from healthy controls ($n=32$). The median copy number is 770 (range, 7×10^2–5×10^4). Similar levels (median, 870; range, 2×10^2–7×10^4) are detected in the perioperative PB of colorectal cancer patients, regardless of stage. CK20 shows similar fluctuation in both controls and patients over follow-up Carcinoembryonic antigen (CEA) mRNA is also detected in 100 per cent of PB samples taken from both healthy controls ($n=47$) (median copy number, 4853, range, 6×10^2–$6{\cdot}8\times10^7$) and perioperative PB from CRC patients (median, 16 921; range, 6×10^2–$7\ 5\times10^7$) Conversely, detection of guanylyl cyclase C (GCC) mRNA appears to be more specific for CRC epithelial cells. Expression is absent in PB of 68/70 healthy controls In contrast, 20/58 colorectal cancer patients express GCC mRNA in their PB at time of surgery 3/38 patients GCC negative at time of surgery become GCC positive during follow-up. Only four patients GCC positive at time of surgery maintain this status for longer than 3 months after operation We are now examining the association between GCC expression in these patients and disease status during follow-up.

Conclusions: GCC may be a molecular marker of circulating micrometastases in colorectal cancer

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Colorectal 007

Angiogenesis in the adenoma–carcinoma sequence

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Aims: The aim of this study was to assess the relationship between microvessel counts in normal mucosa, polyps showing low- and high-grade dysplasia, microinvasive carcinomas arising in polyps (stalk invasion only) and established invasive carcinomas (Duke's stage B/C)

Methods: Five-micrometer sections from paraffin blocks were stained immunohistochemically with a monoclonal antibody JC70 (anti-CD31; Dako, UK) to highlight the microvessels The slides were scanned at magnification ×40 and vascular hot spots identified. Five separate fields were counted at ×400 magnification for each specimen, using the Chalkley grid method.

Results:

Type of lesion	Patients	Mean cumulative vessel count ± s e m
Normal mucosa	57	19 93 ± 0 95
Polyp – low-grade dysplasia	44	24 34 ± 1 08
Polyp – high-grade dysplasia	17	27 65 ± 1 84
Microinvasive carcinoma (stalk)	19	28 05 ± 2 30
Invasive carcinoma (Duke's B/C)	61	32 70 ± 1 47

There is a significant increase in microvessel density (MVD) in invasive carcinomas when compared with all other lesions ($P<0\cdot002$, Mann–Whitney) and a significantly lower MVD in normal mucosa compared with all other lesions ($P<0\cdot0004$, Mann–Whitney). In addition, there is no difference between high-grade dysplasia and microinvasive ($P=0\cdot74$) but significantly increased microvessel density in both these groups when compared with low-grade dysplasia ($P<0\cdot01$)

Conclusions: Increased angiogenesis occurs in several stages during the adenoma–carcinoma sequence, with an increase in MVD occurring in the transition from low- to high-grade dysplasia, and a further increase in the transition from early microinvasive carcinomas to Duke's B/C lesions.

Colorectal 008

Fibronectin receptor expression predicts responsiveness to chemoradiotherapy in rectal cancer

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Aims: The extracellular matrix protein, fibronectin, influences tumour cell proliferation, migration and apoptosis via signalling through the $\alpha5\beta1$ integrin/fibronectin receptor (FnR) We investigated the expression of FnR in rectal cancers and determined its influence on tumour responsiveness to chemoradiotherapy (CRT)

Methods: Thirty-two patients who had undergone CRT (45 Gy 25 fractions + 5-FU/folinic acid) followed by surgical resection for rectal cancer were identified. Pretreatment paraffin-fixed tissue biopsies were sectioned, subjected to microwave antigen retrieval and stained with an anti-FnR antibody using a standard immunohistochemical technique Tumour cell staining was graded by two independent observers and scored as absent = 0, weak = 1, moderate = 2 and strong = 3 Tumour response to CRT was classified as good or poor based on review of the resection specimen histopathology.

Results: Some 44 per cent (14/32) of rectal cancers showed a good response to CRT. Of these, 36 per cent (5/14) had a complete pathological response Where present, normal rectal mucosa showed strong FnR expression There was a general down-regulation in areas of carcinoma, with 53 per cent (17/32) of cases showing absent or weak expression. A positive correlation was seen between FnR expression and response to CRT· 79 per cent (11/14) of good responders had moderate-to-strong staining, while 82 per cent (14/17) of poor responders had absent-or-weak staining ($P<0\cdot001$, χ^2 test)

Conclusions: FnR expression in rectal cancers predisposes to increased responsiveness to CRT. This may have clinical applications for identifying those patients who will benefit from preoperative adjuvant chemoradiotherapy.

Colorectal 009

Colorectal tumour progression is associated with increased expression of matrix metalloproteinases within tumour and plasma

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Aims: In colorectal cancer, increased amounts of matrilysin (MMP-7) are expressed, a potential activator of the latent forms of the gelatinases, MMP-2 and MMP-9, which localize to the invasive margins of tumours. As there are no data in colorectal cancer whether increased tumour expression of these MMPs is reflected within plasma levels, we measured tumour expression and plasma levels of MMP-2 and MMP-9 and correlated this with tumour staging.

Methods: mRNA expression of MMP-2, 7, 9 within 13 colonic adenomas, 50 carcinomas and paired normal tissue was measured using semiquantified reverse transcriptase polymerase chain reaction This was correlated with plasma levels of MMP-2 and MMP-9 and 25 normal controls measured with enzyme-linked immunosorbent assay.

Results: Tumour expression of MMP-7 was significantly elevated in adenomas and all carcinomas compared with normal tissue (means 0·65 *versus* 0·60 *versus* 0·15; $P<0\cdot0001$) In contrast, tumour expression of the MMP-2 and MMP-9 was only elevated in tumours with metastasis or evidence of lymphatic or vascular invasion. This was reflected in plasma levels, although MMP-9 was significantly elevated in all cancers (60·3 ng mL^{-1}) compared with controls (19·7 ng mL^{-1}, $P<0\cdot0001$). Mean levels increased with Duke's stage. Plasma MMP-2 levels were specifically only raised in tumours with invasion or with metastasis ($P<0\cdot01$)

	Tissue MMP-2 (mean ± s e)	Tissue MMP-7 (mean ± s e)	Tissue MMP-9 (mean ± s e)	Plasma MMP-2 (ng mL^{-1}, mean ± s e E)	Plasma MMP-9 (ng mL^{-1}, mean ± s e)
Normal	0·62 ± 0·14	0·15 ± 0·04	0·68 ± 0·14	585·5 ± 43·9	19·7 ± 2·5
Cancer no metastasis	0·49 ± 0·07	0·55 ± 0·05*	0·61 ± 0·05	517·3 ± 50·7	39·4 ± 6·0*
Cancer with metastasis	0·66 ± 0·13	0·65 ± 0·08*	1·00 ± 0·17*	724·5 ± 99·4*	69·1 ± 23·9*
Lymphatic invasion	0·70 ±0·16	0·62 ± 0·07*	1·01 ± 0·20*	749·3 ± 68·4*	51·9 ± 17·0*
Vascular invasion	0·68 ± 0·20	0·59 ± 0·10*	1·18 ± 0·30*	797·4 ± 109*	34·7 ± 6·3*

*Significant increase compared with normal values, $P<0\cdot05$

Conclusions: Elevated expression of MMP-7 is an early event in tumour progression, with MMP-9 levels increasing with cancer stage; MMP-2, particularly in plasma, is only elevated in tumours with metastasis or evidence of lymphatic or vascular invasion Elevated plasma MMP-2 levels may be of clinical value in guiding further adjuvant treatment in Duke's B tumours as this may indicate a higher risk of recurrence or metastasis.

Vascular 010

Does colour duplex improve the accuracy of primary varicose vein surgery?

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Aims: The ability of colour duplex to locate accurately incompetent venous sites has been widely published. However, is it necessary in simple primary varicose vein surgery where clinical and hand-held Doppler examination is almost as good? This study aims to determine this

Methods: A prospective randomized controlled trial was performed on 63 patients undergoing primary varicose vein surgery Randomization was by a sealed envelope system into preoperative colour duplex marking of incompetent venous sites (32 patients) or clinical marking by the operating surgeon ± the use of a hand-held Doppler. Six weeks postoperatively all patients had a colour duplex scan to determine the accuracy of surgery and the presence of residual varicose veins

Results: The table summarizes the results of the surgery performed

Incompetent system	Number of cases	Clinical group (not corrected)	Duplex group (not corrected)	*P*
Long saph system	54	2	3	1
Short saph system	11	3	1	0·545
Perforator veins	63	17	14	0·486

There was also no significant reduction in the number of clinically obvious branch veins ($P=0\cdot21$) between the two groups. There was no association between the grade of operating surgeon and technical success of the surgery.

Conclusions: Colour duplex does not improve the accuracy of primary varicose vein surgery It could therefore be safely omitted in patients undergoing primary varicose vein surgery with an obvious cost benefit

Vascular 011

Dermal oedema in primary superficial venous insufficiency - an evaluation by high-frequency ultrasound

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Aims: To measure dermal oedema in complicated and uncomplicated primary superficial venous insufficiency and assess its relationship to symptoms

Methods: Twenty-two patients with lower-limb varicose veins and seven controls were recruited. A linear analogue scale (0–10) was used to assess the severity of aching, itching, swelling and night cramps. They were examined for the presence of complications, namely eczema, pigmentation, lipodermatosclerosis or ulceration. A 20 MHz ultrasonograph (Dermascan C; Cortex Technology, Denmark) was used to measure dermal echogenicity – the low echogenic part of the image is specific for oedema and was measured as the low echogenic pixel (LEP) density. The distribution of LEPs between upper and lower dermis was also measured (LEPu/l)

Results: Six limbs had complications There were no significant differences in LEP density or LEPu/l between controls and limbs with uncomplicated venous disease. However, the latter had higher total symptom scores (14·5 *versus* 2, $P<0\cdot001$) Limbs with complications had greater LEP densities (164·9 *versus* 27·4, $P=0\cdot006$) and LEPu/l (1·12 *versus* 0·55, $P=0\cdot02$) than those without but there was no difference in total symptom score. Of individual symptoms, only itching correlated with dermal oedema ($r=0\cdot51$, $P<0\cdot01$).

Conclusions: Patients with uncomplicated venous disease do not have excess dermal oedema and it is only with the onset of skin changes that dermal oedema increases, this being preferentially distributed in the upper dermis Itching is related to early skin oedema and may be an indicator of more serious problems in the long term.

Vascular 012

Hydroxyethyl starch solution (eloHAES) reduces renal dysfunction in infrarenal aortic surgery

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Aims: To investigate whether hydroxyethyl starch solution (eloHAES), used as a plasma expander, can reduce the ischaemia–reperfusion-induced renal dysfunction

Methods: Twenty patients undergoing infrarenal aortic surgery were randomly allocated to receive either eloHAES or gelatine (gelofusine) solution. Randomization resulted in two equally matched groups. Urine samples were collected preoperatively (T0), before aortic cross-clamp (T1), after clamp release (T3), subsequently four-hourly for the next 12 h (T4, T5), and daily for two postoperative days (T6, T7). Glomerular permeability was assessed by immunoglobulin G (IgG) and tubular function by α_1 microglobulin (α_1 mg)

Results: The protein leaks were lower in the eloHAES-treated patients, indicating better preservation of glomerular and tubular functions. These differences were statistically significant

Urine protein	Colloid used	Time point T0	T1	T2	T3	T4	T5	T6	T7
IgG	eloHAES	0·58	1·38**	1·44***	0·96***	1·22	0·78	1·08	0·71
	Gelatine	0·41	3·42	5·02	2·84	1·76	1·39	1·18	1·18
α_1 mg	eloHAES	1·22	1·59	2·45**	4·21**	4·59**	6·25	7·91	4·71
	Gelatine	1·33	2·60	7·22	9·60	12·54	11·24	13·67	23·14

*$P<0\cdot05$, **$P<0\cdot02$, ***$P<0\cdot01$, Mann–Whitney test

Conclusions: Compared with gelatine, volume expansion with eloHAES reduces glomerular and tubular dysfunction in the perioperative and early postoperative phases of infrarenal aortic surgery.

Vascular 013

Influence of significant carotid stenosis on cerebral injury following coronary artery bypass grafting (CABG)

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Aims: Although unsupported by clinical trials, a recent survey indicates that 50 per cent of vascular and cardiac surgeons recommend carotid endarterectomy (CEA) for asymptomatic carotid stenoses of >70 per cent in patients requiring CABG In order to determine a possible basis for this strategy, this study assesses markers of cerebral injury in 49 patients with normal carotid arteries (N) and 11 with a >70 per cent stenosis of one or both carotid arteries (C) undergoing CABG.

Methods: Serum S100 levels (protein released from glial cells following cerebral injury) were measured before, during and for 5 days after CABG. A trained psychologist assessed alterations in cognitive function (CF) from baseline using a computerized battery of seven nonverbal neuropsychometric tests (CANTAB) at 5 and 90 days postsurgery

Results: Peak S100 levels (mean ± s d) occurred when coming off cardiopulmonary bypass but were similar in N ($4\cdot34\ \text{mmol}\ \text{L}^{-1} \pm 2\cdot36$) and

C (4·77 ± 2·30). Further, there were no differences (N *versus* C) prebypass (0·39 ± 0·28 *versus* 0·23 ± 0·21), going on bypass (0·89 ± 0·83 *versus* 0·99 ± 0·95), bypass + 30 min (1·54 ± 1·12 *versus* 1·50 ± 1·11), and at 24 h (0·53 ± 0·22 *versus* 0·42 ± 0·26) or 120 h postsurgery (0·14 ± 0·09 *versus* 0·12 ± 0·05). Neuropsychometric testing also failed to demonstrate a difference between the groups in seven domains of CF (executive function, working memory), although 50 per cent of both groups had a demonstrable neuropsychometric deficit. No postoperative strokes occurred.

Conclusions: This study shows no evidence of subclinical brain ischaemia and cerebral injury in patients with asymptomatic carotid disease undergoing CABG, so does not lend support to routine CEA in such patients.

Vascular 014

Long-term reliability of the Vanguard endovascular device

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Aims: There have been reports of long-term failure of the Vanguard modular bifurcate stent graft device. The aim of this paper was to examine the durability of the Vanguard system for abdominal aortic aneurysm (AAA) repair

Methods: Between 1995 and 1998, 54 patients with infrarenal AAA underwent endovascular repair with the Vanguard system at a single centre. Postoperatively, patients were assessed at regular intervals by contrast-enhanced CT scans and plain films. Angiography was performed for suspected endoleak or iliac limb occlusion and, if confirmed, endovascular treatment was utilized wherever possible. Life table analysis was performed for success of AAA exclusion and graft limb patency

Results: Graft deployment was successful in all 54 patients. Eight endoleaks have been identified, four early (<30 days) and four late (30 days–3 years). Seven of these were treated endovascularly (one coil embolization, six additional endoluminal grafts). One patient required surgical treatment with aortic banding of the proximal neck. There have been six iliac limb occlusions. Two were treated radiologically (one subsequently requiring iliofemoral grafting), three required femoro-femoral crossover grafts and one received no treatment. Life table analysis shows a 3-year primary exclusion rate of 82 per cent and secondary exclusion rate of 96 per cent. Primary iliac limb patency is 86 per cent and secondary patency 90 per cent at 3 years

Conclusions: This paper shows that, with additional endovascular or surgical measures where required, the Vanguard system is durable and life table analysis appears to confirm its reliability when compared with other devices

Vascular 015

Oxygen requirements improved by endovascular AAA repair

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Aims: Perioperative oxygen requirements in patients undergoing aneurysm surgery may have significant implications for subsequent recovery. The aim of this paper is to study systemic oxygen extraction during abdominal aortic aneurysm (AAA) repair, comparing open with an established endovascular technique

Methods: Twenty patients underwent surgery for an infrarenal AAA. Repair was either open ($n = 10$) or endovascular using a bifurcate stent graft ($n = 10$). Each patient received a standard anaesthetic by a consultant anaesthetist using intermittent positive pressure ventilation. All had a peripheral arterial line and a pulmonary artery balloon catheter inserted after induction of anaesthesia. Arterial and mixed venous blood samples were taken before aortic occlusion and 1 h after restoration of blood flow. Sample analysis for haemoglobin concentration along with oxygen tension and saturation was made. Calculation of oxygen content (arterial C_aO_2 and mixed venous C_vO_2) and thus fractional oxygen extraction (FOE) could be made. $FOE = (C_aO_2 - C_vO_2)/C_aO_2$. Statistical analysis by Wilcoxon signed ranks.

Results:

	Preocclusion FOE (mean ± s.d.)	Postocclusion FOE (mean ± s.d.)	*P*
Open	0·25 ± 0·05	0·37 ± 0·09	0·007
Endovascular	0·26 ± 0·05	0·25 ± 0·07	0·09

Conclusions: There is significant increase in systemic oxygen extraction following aortic crossclamping, which is not seen during endovascular graft deployment. This has implications for patients with comorbid conditions and, thus, the applicability of endovascular AAA repair

Vascular 016

How exercise training improves walking distance in claudicants

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Aims: To determine how exercise training improves maximum walking distance (MWD) of claudicants

Methods: Twenty-three patients successfully completed the training programme for 3 months. Pre- and post-training MWD, heart rate, oxygen consumption, common femoral artery blood flow (CFA-BF), venous lactate were measured

Results: Analysis was by paired *t*-test. MWD improved from 133 ± 60·7 to 242·5 ± 137·1 m, $P < 0·05$

	Pre-training	Post-training	*P* value
CFA-BF (measured by duplex scan)			
Rest (mL min^{-1})	120 ± 70	178 ± 90	0·054
Peak (after calf exercise for 2 min)	269 ± 122	305 ± 183	0·60
2 min after exercise	186 ± 155	197 ± 143	0·90
Exercise phase (walking on a treadmill at an identical workload)			
O_2 used (mL kg^{-1} m^{-1})	0·355 ± 0·076	0·323 ± 0·062	<0·05
Average HR (beats min^{-1})	108·4 ± 18·5	97·8 ± 16·1	<0·05
Venous lactate (mmol L^{-1})			
Rest	1·15 ± 0·51	1·06 ± 0·37	0·51
1 min after walking to MWD	1·75 ± 0·71	1·35 ± 0·61	<0·05
6 min after walking to MWD	1·49 ± 0·58	1·15 ± 0·62	<0·05

Conclusions: Improvement in MWD was not a result of an increased blood flow. It could be a result of improvement in cardiac functions, aerobic metabolism and reduction in oxygen cost of exercise.

Vascular 017

Near-infrared spectroscopy (NIRS) to measure muscle ischaemia during claudication

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Aims: Intermittent claudication is frequent, affecting 5 per cent of men over 50. As very little is known about the severity of muscle ischaemia on

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exercise, we evaluated NIRS. a noninvasive method, to assess haemoglobin oxygenation and perfusion in claudicants.
Methods: Thirty subjects were examined (i) 16 claudicants, (ii) seven similar age and (iii) seven <30 years healthy controls. Calf muscle oxyhaemoglobin (O_2Hb), deoxyhaemoglobin (Hhb), oxygenation index (HbD) (O_2Hb-HHb) and total haemoglobin (tHb) were measured by NIRS during and after walking on a treadmill at $3{\cdot}2\,\mathrm{km\,h^{-1}}$ and a gradient of 10° for 7 min or until stopped by claudication. ABPI was also measured before and following exercise.
Results: During exercise, O_2Hb fell markedly in claudicants by $119{\cdot}0 \pm 20{\cdot}9\,\mu\mathrm{mol\,cm^{-1}}$ tissue compared with modest falls in elderly controls at $28{\cdot}8 \pm 15{\cdot}6$ and in young controls at $6{\cdot}3 \pm 18{\cdot}6$ ($P<0{\cdot}05$). This was associated with a greater rise in HHb of $131{\cdot}0 \pm 33{\cdot}3$ in claudicants compared with $30{\cdot}1 \pm 9{\cdot}9$ and $26{\cdot}1 \pm 8{\cdot}2$ in elderly and young controls respectively ($P<0{\cdot}05$) The HbD, which indicates oxygen extraction, was $-249{\cdot}1 \pm 50{\cdot}7$ in claudicants compared with $-62{\cdot}8 \pm 8{\cdot}3$ in elderly, and only $-29{\cdot}8 \pm 16{\cdot}1$ in young controls ($P<0{\cdot}05$). There was no significant rise in tHb, analogous to blood flow, in claudicants when compared with controls.
Conclusions: Oxygen extraction in exercising calf muscle is profound in claudicants, suggesting more severe ischaemia than expected. Changes in NIRS may be used to distinguish claudication from other leg pains and evaluate therapies to improve tissue perfusion.

Vascular 018

Exercise in claudicants is associated with thrombin generation, systemic fibrinolysis but not endothelial cell injury

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Aims: Claudicants exhibit a 2–3-fold increase in fatal thrombotic events compared with an age–sex-matched nonclaudicant population This study aimed to determine whether exercise in claudicants leads to endothelial cell (EC) injury and/or a procoagulant state.
Methods: Peripheral venous blood was drawn from 24 claudicants and 12 age–sex-matched controls prior to and immediately, 1, 5, 10, 20, 40 and 60 min after treadmill exercise. EC injury was determined by von Willebrand factor (vWF); thrombin generation by prothrombin fragment (PF) 1+2 and thrombin-antithrombin (TAT); and fibrinolysis by tissue plasminogen activator (tPA) and plasminogen activator inhibitor (PAI-1) activity.
Results: At baseline, claudicants had higher levels of TAT (median [IQR], 3·35 [1·55–10·41] *versus* 1·70 [0·32–3·62] $\mu\mathrm{g\,L^{-1}}$, $P<0{\cdot}02$, Mann–Whitney) and vWF (1·61 [0·70–2·43] *versus* 0·62 [0·15–1·63], $P<0{\cdot}04$, MW) Controls did not exhibit a significant change in any marker following exercise. In claudicants, exercise led to a significant rise in TAT (3·35 [1·55–10·41] *versus* 39·05 [21·71–53·91] $\mu\mathrm{g\,mL^{-1}}$, $P<0{\cdot}001$, Kruskal–Wallis) and tPA activity (3·0 [1·6–4·1] *versus* 6·2 [3·8–8·0] $\mathrm{IU\,mL^{-1}}$, $P=0{\cdot}005$, KW) and a significant fall in PAI-1 activity (8·5 [4·3–12·5] *versus* 6·3 [2·0–10·3] $\mathrm{IU\,mL^{-1}}$, $P<0{\cdot}05$, KW). PF 1+2 and vWF did not change
Conclusions: Exercise in claudicants is not only associated with thrombin generation but also with systemic fibrinolysis The pathogenesis of these coagulation changes remains unexplained but does not appear to be associated with EC injury.

Vascular 019

Suitability of treadmill-based exercise training for intermittent claudication

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Aims: The optimal exercise programme for treatment of intermittent claudication remains undefined and some programmes advocate the use of treadmill walking (TW) We examine the ability of patients to use TW for exercise training
Methods: Consecutive series of patients referred with IC were assessed. The diagnosis of IC was defined by appropriate history, correct response to the Edinburgh claudication questionnaire and ABPI<0·9. Identified claudicants underwent a recognized protocol that included a period of rest for 15 min, followed by 5 min of warm-up exercise before walking on a treadmill fixed at $3{\cdot}2\,\mathrm{km\,h^{-1}}$, 0 per cent grade for a maximum of 10 min with constant ECG monitoring The initial claudication (ICD), absolute claudication (ACD) distances and the causes for premature termination of the programme other than for the development of maximum claudication pains were noted.
Results: Some 67 new claudicants were recruited. Median age was 68 years (range, 42–86) with 73 per cent males. Median verbally estimated walking distance was 183 m (range, 9–1829). Median ICD was 92 m (range, 24–533) and the median ACD was 142 m (range, 48–533). Thirteen patients (19 per cent) completed the 10-min walk without claudication pains. Eighteen patients (32 per cent) required premature termination of the TW programme before the onset of claudication caused by back pain (eight), chest pain (three), ischaemic ECG changes (one), shortness of breath (four) and joint pain (two) The Edinburgh claudication questionnaire failed to exclude the eight patients with back pain.
Conclusions: This study suggests that treadmill-based exercise training programmes will not be suitable for at least one-third of patients with IC and its inclusion in future trials to determine the optimal exercise programme for IC is not recommended.

Vascular 020

The importance of flow distribution and anastomotic configuration in infrainguinal arterial reconstruction

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Aims: This research was designed to identify the distribution of flow at the distal anastomosis of *in vivo* bypass grafts, and to study its influence on haemodynamics within different anastomotic configurations
Methods: Intraoperative flow volumes within distal and proximal outflow components of the recipient artery were measured, using a perivascular flowprobe and an ultrasonic flowmeter, in patients undergoing infrainguinal bypass These data were then incorporated into laboratory-based flow visualization studies in models of Miller cuff and end-to-side anastomoses, perfused under physiological conditions.
Results: Nineteen patients (mean age, 67·3 years) underwent infrainguinal bypass for critical ischaemia (74 per cent), and debilitating claudication (26 per cent), using bypass conduits of vein (63 per cent) and PTFE (37 per cent), anastomosed to above and below knee popliteal arteries (52 per cent), and tibial vessels (48 per cent) The mean volume flow in distal and proximal outflow vessels was $100\,\mathrm{mL\,min^{-1}}$ and $37\,\mathrm{mL\,min^{-1}}$, respectively, giving a mean percentage ratio of 76 24 (range, 100 0 to 38·62). Similar results were found when flow volumes were stratified for bypass to popliteal and to tibial vessels. Published studies refer to *in vitro* distributions of 50:50 and 100.0. These are significantly different from the mean *in vivo* distribution we found, $P<0{\cdot}0001$ (one sample *t*-test). In the Miller cuff, flow visualization identified minor differences in flow patterns between various distributions, with 100 per cent distal flow creating a less

organized vortex with helical components at the toe The end-to-side anastomosis, in contrast, showed significant changes. At distributions of 50:50 and 75:25, large areas of flow separation were identified in the graft hood, with static points of flow division along the recipient artery floor. A distribution of 100:0 created a less static flow division point and a vortical structure This, however, was less extensive in size and duration than that observed in the cuff

Conclusions: Flow distribution is an important parameter in determining the haemodynamics of any distal anastomosis, and theoretical and laboratory models should incorporate the range of distributions we identified, with a mean of 75 per cent distal and 25 per cent proximal Flow patterns within the Miller cuff appear to be more resilient to the influence of flow distribution than those in end-to-side anastomosis, which may relate to a potential clinical benefit.

Vascular 021

Prospective study of the incidence of abdominal aortic aneurysms in patients with intermittent claudication

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Aims: The aims of this prospective study were to assess whether claudicants had a higher incidence of abdominal aortic aneurysms (AAA) than the 1–3 per cent found in the general population over 65 years

Methods: Over a 46-month period, 517 claudicants, 338 men and 179 women, median age 68 (range, 26–97) years, underwent upper abdominal B mode ultrasound A maximum AP diameter of 3 cm or more was used to define an aneurysm

Results:

	Men			Women		
Age (years)	*n*	AAA	(%)	*n*	AAA	(%)
<54	47	0	(0 0)	14	0	(0 0)
55–59	57	3	(5 3)	12	0	(0 0)
60–64	49	8	(16 3)	20	3	(15 0)
65–69	53	7	(13 2)	25	0	(0 0)
70–74	61	12	(19 7)	41	2	(4 9)
75–79	56	12	(21 4)	43	4	(9 3)
>80	9	3	(20 0)	24	2	(8 3)
Total	338	45	(13 3)	179	11	(6 2)

Of the 45 AAA detected in the men, AP diameter was greater than 4 cm in 19 patients and greater than 5 cm in eight patients. Of the 11 AAA detected in the women, AP diameter was greater than 4 cm in three patients with none greater than 5 cm.

Conclusions: Claudicants have a higher incidence of AAA than the general population, and routine ultrasonography should be considered, especially when the patient is male and 55 years or older

Breast/Oncology 001

Prospective comparison of spiral CT and gadolinium-enhanced MRI in the staging of suspected pancreatic and periampullary tumours

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Aims: To prospectively compare spiral CT and gadolinium-enhanced MRI for staging of pancreatic and periampullary tumours

Methods: Patients referred to a single specialist pancreatic clinic with a clinical suspicion of pancreatic or periampullary tumour had both contrast-enhanced spiral CT and gadolinium-enhanced MRI to set protocols. Liver or nodal metastases were confirmed histologically and vascular involvement at laparotomy. Paired comparisons were made using McNemars test with significance defined at the 0·05 per cent level

Results: Sixty-eight patients entered the study and had final histological confirmation of the diagnoses. All had spiral CT and MRI attempted. MRI was incomplete in 3 (4 per cent) Sixteen patients (24 per cent) had obvious extensive disease either posteriorly or with liver metastases and one patient declined surgery Of the remaining 52 patients who had a laparoscopy, 16 (31 per cent) had evidence of metastases, the remaining 36 proceeding to laparotomy, 23 of whom (64 per cent) had a pancreatic resection and 13 (36 per cent) had biliary enteric bypasses. Final histological diagnoses were 55 pancreatic ductal carcinomas, eight ampullary carcinomas, two chronic pancreatitis and two serous cystadenomas A focal mass was detected in 53 patients (78 per cent) by MRI and in 51 patients (75 per cent) by spiral CT. The sensitivity and specificity for liver and lymph node metastases and superior mesenteric artery (SMA) and superior mesenteric/portal vein (SMV/PC) are shown in the table.

	Spiral CT		MRI	
	Sensitivity	Specificity	Sensitivity	Specificity
Liver metastases	70% (7/10)	93% (39/42)	67% (6/9)	93% (37/40)
LN metastases	33% (4/12)	84% (16/19)	9% (1/11)	100% (17/17)
SMA	50% (2/4)	100% (29/29)	67% (2/3)	100% (21/21)
SMV/PV	53% (9/17)	100% (19/19)	65% (11/17)	94% (16/17)

No significant differences were found in any category by McNemar's test for paired proportions.

Conclusions: MRI is as accurate as spiral CT in the staging of pancreatic and periampullary tumours.

Breast/Oncology 002

Experimental model of hepatic fibrosis and liver metastasis

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Aims: We have shown in a meta-analysis of human data that the cirrhotic liver is protected from the development of metastases. Therefore, with ethical and Home Office approval, we developed an animal model of colorectal hepatic metastasis in normal and cirrhotic rats to test the null hypothesis of no difference between cirrhotics and controls.

Methods: Female BD IX rats were allocated as either controls ($n=19$) or for induction of cirrhosis ($n=21$) Cirrhosis was induced by up to 20 gavages of 20 per cent carbon tetrachloride solution in household oil. Animals were designated as cirrhotic when they developed clinical signs of liver failure and with the onset of hepatic ascites (detectable by sudden weight gain) Cirrhotic animals and controls had liver metastases induced by injection of 10^7 colon cancer cells (DHDK-12) into their portal veins at laparotomy. Four weeks after surgery the animals were killed and underwent postmortem examination to assess the tumour load (by weight and point counting) in the liver and lungs Liver tissue was collected for histological confirmation of cirrhosis

Results: Absolute protection was not seen. control animals and cirrhotics all developed metastases. The cirrhotic animals developed significantly less liver metastases (Mann–Whitney U test, $P=0\cdot01$). The median weight of the cirrhotic livers with tumour was 12 5 g (range, 7·9–25·6 g) and the control median was 22 5 g (range, 9·4–28·3 g). Two patterns of disease emerged. None of the controls developed macroscopic lung metastases; conversely, in the cirrhotic group, lung metastases were frequently seen (Fisher's exact test, $P<0\ 001$).

Conclusions: This animal study is the first model to support the hypothesis that the cirrhotic liver is protected from the development of metastases, the null hypothesis is rejected The increase in detected pulmonary metastases suggests that veno-venous shunting may explain the difference.

Breast/Oncology 003

Leptin and its relation to weight loss, *Ob* gene expression and the acute phase response

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Aims: Cachexia is a complex syndrome, characterized by a decrease in food intake and weight loss, which is common in patients with cancer and inflammation. The study is aimed at elucidating the possible role of leptin in cachexia through examining the relationship between leptin and body fat, weight loss, and the acute phase protein response.

Methods: Thirty-three patients undergoing elective colorectal surgery (24 for cancer) had their height, weight, pre-illness weight and weight-loss recorded Blood was analysed for C-reactive protein (CRP), TNFα, soluble TNF receptors 55 and 75, IL-6, and plasma leptin level Fat was excised at surgery for analysis of subcutaneous and omental leptin mRNA expression (*Ob* gene) by quantitative PCR. Body mass index (BMI), total body water, lean body mass, and fat mass were calculated from anthropometric measurements using standard equations Nonparametric tests were used for statistical analysis and data are expressed as median (min-max).

Results: A positive correlation was found between leptin level and fat mass ($r=0\cdot625$, $P<0\ 01$). Leptin level in weight-losing patients was significantly lower ($P<0\cdot05$) than in nonweight-losing patients (3 9 ng mL^{-1} (0·9–39·7) *versus* 8 9 ng mL^{-1} (2 1–51 5)). Leptin level was found to be inversely related to percentage weight loss ($r=-0\cdot485$, $P<0\ 01$) When leptin levels were corrected for fat mass, patients who had an acute phase protein response (CRP $\geqslant$ 10 mg L^{-1}) had significantly higher ($P<0\cdot05$) leptin levels than those who had no acute phase protein response (1 ng mL^{-1} (0·5–1·6) *versus* 0·3 ng mL^{-1} (0·1–2·5)). Serum TNFα and IL-6 levels were also significantly higher in patients having an acute phase protein response A positive correlation was found between leptin level and omental leptin mRNA ($r=0\ 629$, $P<0\cdot05$) but not subcutaneous leptin mRNA ($r=0\ 291$, $P<0\ 386$)

Conclusions: The correlation between plasma leptin level and fat mass, together with its inverse relation with percentage weight loss indicate that the decrease in leptin in weight-losing individuals is secondary to loss of fat. However, the finding that leptin levels were relatively high in patients with an acute phase response suggests leptin itself may contribute towards anorexia and hypermetabolism in these patients.

Breast/Oncology 004

Lipopolysaccharide enhances tumour cell adhesion and invasion through a β1 integrin mechanism

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Aims: β1 integrins play a crucial role in supporting tumour cell growth in, attachment to, migration on, and invasion in the extracellular matrix proteins. Lipopolysaccharide (LPS) has been shown to be a causative factor in surgically induced tumour metastasis in an *in vivo* animal model This study was designed to test the hypothesis that LPS can enhance tumour cell metastatic potential on extracellular matrix proteins through β1 integrin pathways
Methods: Human colorectal tumour cell lines SW480 and SW620 were treated with either LPS (0·1 μg mL^{-1}) alone or LPS in the presence of recombinant soluble CD14 (rsCD14, 0·2 μg mL^{-1}). Expression of β1 integrins and membrane CD14 (mCD14) was detected by flow cytometry. Tumour cell adhesion to extracellular matrix proteins and *in vitro* tumour cell invasion through Matrigel chambers were assessed
Results:

	Medium	LPS	LPS + rsCD14	LPS + rsCD14 + 4B4	LPS + rsCD14 + 6S6
Adhesion (%)	15 ± 4·0	17 ± 4·7	39 ± 9·8*	18 ± 6·1†	19 ± 4·9†
Invasion (numbers)	21 ± 5·7	19 ± 4·3	57 ± 10*	31 ± 6·5†	27 ± 6·2†

Data = mean ± s d , $n = 6$, Stats ANOVA, *$P < 0·05$ *versus* medium and LPS alone, †$P < 0·05$ *versus* LPS + rsCD14

Both SW480 and 620 constitutively expressed high levels of β1 subunit SW480 and 620 did not express mCD14. However, LPS treatment in the presence of rsCD14 significantly up-regulated SW480 β1, α2 and α3 expression and SW620 β1, α3 and α6 expression ($P < 0·05$, *versus* culture medium and LPS alone). Furthermore, LPS in the presence of rsCD14 significantly enhanced tumour cell attachment to extracellular matrix proteins, and strongly promoted tumour cell invasion through Matrigel ($P < 0·05$ *versus* culture medium and LPS alone). LPS alone had no effect on tumour cell adhesion and invasion. Two anti-β1 blocking mAbs (4B4 and 6S6), but not anti-α1, anti-α2, anti-α3 and anti-α6 blocking mAbs significantly attenuated LPS plus rsCD14-induced tumour cell adhesion and invasion.
Conclusions: These results provide direct evidence that, although SW480 and 620 do not express mCD14, LPS in the presence of rsCD14 can up-regulate β1 integrin expression and subsequently promote tumour cell adhesion and invasion Moreover, LPS-induced tumour cell adhesion to and invasion in extracellular matrix proteins is β1 subunit dependent.

Breast/Oncology 005

Antiangiogenic therapy for bone metastases is detrimental to normal bone metabolism

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Aims: Antiangiogenic agents are an attractive option for treatment of malignant disease, in particular, the highly vascular bone metastasis. Fumagillin (TNP470), a naturally occurring antibiotic, is presently under clinical trial in patients with advanced metastatic disease We hypothesized that TNP470 would attenuate normal bone metabolism at doses proposed for therapeutic intervention
Methods: Primary human osteoblasts (OB) were isolated from femoral heads excised during hip arthroplasty and endothelial cells (EC) from fresh human umbilical vein. These were cultured for 24 h in control culture medium or medium supplemented with TNP470 (1 pg mL^{-1}– 1 mg mL^{-1}) Cell proliferation, viability, apoptosis and necrosis were determined by 5 bromo-2-deoxyuridine DNA labelling, tetrazolium bioreduction, cytosolic histone-associated DNA fragmentation and lactate dehydrogenase assay respectively
Results: Data illustrate mean ± s.e.m. and $n = 4$ experiments in each case.

		TNP 470			
	Control	1 pg mL^{-1}	10 ng mL^{-1}	1 μg mL^{-1}	1 mg mL^{-1}
EC viability (% control)	100 ± 1	99 ± 1	85 ± 2*	64 ± 3*	42 ± 2*
OB viability (% control)	100 ± 2	99 ± 2	66 ± 4*#	32 ± 3*#	26 ± 1*#
EC proliferation (% control)	100 ± 2	100 ± 1	96 ± 2*	84 ± 3*	42 ± 4*
OB proliferation (% control)	100 ± 3	99 ± 2	68 ± 3*#	32 ± 5*#	18 ± 3*#
EC apoptosis (% cells)	16 ± 2	18 ± 1	24 ± 2*	46 ± 3*	50 ± 4*
OB apoptosis (% cells)	22 ± 1#	23 ± 3#	57 ± 2*#	66 ± 2*#	70 ± 2*#
Necrosis (% cytoxicity)	2 ± 0·5	3 ± 1	8 ± 1·5*	24 ± 2*	60 ± 5*
Necrosis (% cytoxicity)	2 ± 1	4 ± 2	14 ± 3*#	38 ± 6*#	78 ± 4*#

ANOVA was employed for statistical analysis, **versus* control medium, #*versus* endothelial cells, $P < 0·05$ was considered significant

Conclusions: Fumagillin induces cell apoptosis or necrosis in a concentration-dependent fashion Osteoblasts demonstrated greater sensitivity to TNP470 at significantly lower doses (10-fold) than did endothelial cells. While antiangiogenic agents are attractive for treatment of bone metastases, we must be ever-vigilant of their effects on normal cell turnover.

Breast/Oncology 006

Bone metastases in breast cancer – a role for osteoblasts?

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Aims: Understanding the mechanisms of bone metastases is crucial to improving therapy for advanced breast cancer. Secondary malignant deposits are characterized by relative hypoxia of native bone cells We hypothesized that osteoblasts in this hypoxic environment would modulate breast cancer metastases
Methods: Primary human osteoblasts were cultured in hypoxia (2 per cent O_2) and normoxia (21 per cent O_2) for 6, 12 and 24 h. Production of angiogenic cytokines vascular endothelial growth factor (VEGF) and fibroblast growth factor (bFGF) were measured using an enzyme-linked immunosorbent assay The human metastatic breast cancer cell line MDA MB 231 was then cultured in control medium or hypoxic osteoblast conditioned medium (OB CM), with and without neutralizing monoclonal antibody (mAB) to VEGF (0·3 μg mL^{-1}). Endothelial cells were isolated from fresh human umbilical vein and cultured to a monolayer Tumour cell proliferation, viability and transendothelial migration were then determined by 5 bromo-2-deoxyuridine DNA labelling, tetrazolium bioreduction and under light microscopy respectively
Results: Data illustrate mean ± s e m and $n = 4$ experiments in each case.

	21%			2%		
	6 h	12 h	24 h	6 h	12 h	24h
OB VEGF (pg mL^{-1})	231 ± 72	343 ± 57	590 ± 45	239 ± 54	453 ± 12*	903 ± 128*
OB bFGF (pg mL^{-1})	37 ± 2	49 ± 3	53 ± 6	37 ± 2	47 ± 6	54 ± 4
MDA MB 231	Control	Hypoxic OB CM	OB CM + mAB VEGF			
Proliferation (% control)	100 ± 4	246 ± 11#	137 ± 9#			
Viability (% control)	100 ± 7	140 ± 3#	120 ± 2#			
		Control	Hypoxic OB CM			
Transmigration (% cells migrated)	3 h	11 ± 2	20 ± 1#			
	6 h	12 ± 1	37 ± 4#			

ANOVA was employed for statistical analysis, **versus* normoxia, #*versus* control, $P < 0·05$ was considered significant

Conclusions: Osteoblasts produce selective angiogenic cytokines (VEGF and not bFGF) under hypoxic conditions. These cells enhance tumour cell transendothelial migration, proliferation and viability, primarily via VEGF-mediated mechanisms. These data provide a putative role of osteoblasts in bone metastases development and suggest alternative therapeutic targets for the treatment of advanced breast cancer

Breast/Oncology 007

Characterization of the mitogenic actions of parathyroid hormone-related protein in MCF-7 breast carcinoma cells

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Aims: Parathyroid hormone-related protein (PTHrP) expression in primary breast cancers is strongly linked with the subsequent development of bone metastases and hypercalcaemia. In the present study, we aimed to characterize the mitogenic actions downstream of the G protein-coupled PTHrP receptor

Methods: Using MCF-7 cells stably transfected with either the wild-type PTHrP receptor (^{WTR}) or a mutant receptor that exhibits constitutive, ligand-independent activation (^{T410p}), cAMP, thymidine uptake and ERK MAP kinase responses to PTHrP 1-34 stimulations were assayed using RIA and western blotting

Results: Stimulation of MCF-7^{WTR} cells with 500 ng mL^{-1} PTHrP 1–34 generated a significant 5–6-fold elevation in intracellular cAMP levels (basal, 42 ± 7 pmol well^{-1}; PTHrP, 228 ± 55 pmol well^{-1}) and increased DNA synthesis by 37 ± 8 per cent above basal. By contrast, identical treatment of MCF-7 vector cells failed to increase significantly intracellular cAMP or DNA synthesis. MCF-7^{T410p} cells exhibited elevated basal cAMP levels (74 ± 25 pmol well^{-1}) which were further elevated by PTHrP to 191 ± 55 pmol well^{-1} PTHrP also increased DNA synthesis in MCF-7^{T410p} cells (24 ± 7 per cent above basal). All the above effects were mimicked by the cAMP agonist forskolin. Treatment of MCF-7 vector cells with 2 per cent serum increased DNA synthesis by 78 ± 28 per cent. Identical treatment of MCF-7^{WTR} and MCF-7^{T410p} cells resulted in significantly higher increases in DNA synthesis (122 ± 28 and 191 ± 77 per cent respectively) PTHrP also induced a small apparent activation of ERK MAP kinases, which was mimicked by forskolin Interesting, PTHrP potentiated (by two fold) the activation of MAP kinase induced by both EGF and IGF-1.

Conclusions: These studies show that increased expression of the PTHrP receptor in breast cancer cells increases their responsiveness to the mitogenic actions of not only PTHrP but also serum growth factors, and these effects appear to be mediated via a cAMP-dependent signalling pathway The ability of PTHrP to potentiate MAP kinase activation by peptide growth factors additionally suggests that this pathway may serve to integrate mitogenic signals derived from G protein-coupled receptors and tyrosine kinase receptors in breast cancer cells.

Breast/Oncology 008

Bacterial wall components enhance tumour cell metastatic potential

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Aims: Bacterial translocation and endotoxaemia may enhance tumour growth following surgery for malignant disease Endotoxin (LPS), a bacterial wall component, enhances tumour metastasis *in vivo*, and tumour cell proliferation and transendothelial cell migration *in vitro*. We hypothesize that bacterial lipoprotein (BLP), another bacterial wall product, has similar effects on tumour growth and metastasis.

Methods: The human metastatic breast cancer cell line MDA MB 231 was incubated with LPS (0·01–10 µg mL^{-1}) and BLP (0·001–1 µg mL^{-1}) Cell proliferation was determined using 5 bromo-2-deoxyuridine DNA labelling. Tumour cells were examined for the expression of integrins mediating transmigration (β2 and avb3), using flow cytometry Tumour cell transendothelial migration was examined following pretreatment of either the tumour cells or the endothelial cell monolayer with LPS (1 µg mL^{-1}) and BLP (0·1, 1 µg mL^{-1}). Data are expressed as mean ± s e m. (n = 4 experiments).

Results:

Cell proliferation	Control	LPS (10 ng mL^{-1})	BLP (10 ng mL^{-1})
12 h	100+3·7	110+2*	124+1·6*
24 h	100+6	136+1·6*	147+0·5*

ANOVA was employed for statistical analysis, *$P<0·05$ was considered significant

Incubation of tumour and endothelial cells in LPS (1 µg mL^{-1}) and BLP (0·1–1 µg mL^{-1}) resulted in a significant increase in tumour cell transmigration at 3 and 6 h ($P<0·05$). MDA MB 231 did not constitutively express β2 integrins. Expression of αvβ3 was not enhanced following 6, 12 or 18 h incubation in BLP

Conclusions: Bacterial lipoprotein significantly enhanced both tumour cell proliferation and transmigration, similar in effect to lipopolysaccharide. Enhanced tumour cell transmigration in the absence of altered integrin expression suggests an integrin-independent pathway This concept is supported by the findings of the effect of these bacterial wall components on the endothelial cell monolayer. Thus, it appears that other components of the bacterial cell wall may be as important as LPS in the stimulation of metastatic tumour growth following surgery.

Breast/Oncology 009

Angiogenic response to hypoxia is greater in benign than malignant primary breast cultures

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Aims: Tumour hypoxia is thought to represent a poor clinical outcome, possibly secondary to up-regulation of angiogenic growth factors Our aim in this study was to assess the influence of hypoxia on the production of angiogenic cytokines, vascular endothelial growth factor (VEGF) and transforming growth factor β1 (TGFβ1) in stromal and epithelial primary cultures of benign and malignant breast samples.

Methods: Protein expression of VEGF and TGFβ1 was analysed by ELISA from media of both stromal and epithelial components of benign (n = 8) and malignant (n = 13) primary breast cultures grown under hypoxic (94 per cent N_2, 5 per cent CO_2, 1 per cent O_2) and normoxic conditions

Results:

	Hypoxia		Normoxia	
	Stromal	Epithelial	Stromal	Epithelial
Benign				
TGFβ1	165·3 (44·6–423·5)	10·4 (1·8–32·8)	67·8 (19·2–223·6)	8·4 (6·0–26·8)
VEGF	227·5 (89·6–389·8)	99·5 (58·6–218·8)	91·6 (52·0–152·0)	39·4 (12·8–80·9)
Malignant				
TGFβ1	108·9 (41·6–200·6)	1·8 (1·2–19·6)	91·7 (42·9–219·8)	1·2 (1·0–20·2)
VEGF	174·8 (91·7–252·7)	164·1 (117·9–390)	119·2 (56·9–210·4)	69·4 (47·8–108·9)

Data median (interquartile range) pg mL^{-1} µg^{-1} protein

VEGF and TGFβ1 were detected in all samples, epithelial and stromal production of both cytokines was equal in malignant cultures There were significantly higher levels of VEGF ($P=0\cdot02$, Mann–Whitney *U*) and TGFβ1 ($P=0\cdot018$) in the stromal compared with epithelial element of the benign breast tissue cultures. A significant elevation in VEGF production was seen in both stromal ($P=0\cdot028$) and epithelial ($P=0\cdot025$) cultures of benign cells grown in hypoxic conditions In the tumour group, only epithelial samples showed increased VEGF levels under hypoxic conditions ($P=0\cdot001$). Paradoxically, the angiogenic response to hypoxia was greater in benign rather than malignant stromal cultures (VEGF $P=0\cdot03$, TGFβ1 $P=0\cdot04$, Wilcoxon analysis).

Conclusions: These data for the first time demonstrate that angiogenic cytokine production in response to hypoxia was greater in benign tissue, suggesting that paracrine regulation of angiogenesis in solid tumours may be of greater significance than local chemical effects. These results may have implications for antiangiogenic therapy.

UGI 001

Effect of surgical workload on outcome from resection for cancer of the oesophagus and cardia

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Aims: To assess the effect of surgical workload on outcome from cancer of the oesophagus and cardia in order to inform the debate about organization of upper GI cancer services in the UK.

Methods: We studied elective and emergency resection for oesophageal and cardia cancer in the West Midlands during the 5-year period 1992–96. The outcome from surgery was assessed with respect to the number of resections performed by individual surgeons.

Results: Sixty-four surgeons performed a total of 1093 resections, of which 61 per cent were for oesophageal cancer with 8 per cent being managed as an emergency and 62 per cent with stage III/IV disease Six surgeons performed more than 50 cases each (frequent group), 17 surgeons performed between 10 and 49 cases (regular group) and 41 surgeons performed up to nine cases (infrequent group) in the 5-year period

					Mortality rate (%)		
Group	No of cases	% as cardia	% as elective	% as stage I/II	30 day	60 day	Survival (%) 2-year
Infrequent	108	47	88	32	19	24	21
Regular	458	42	93	37	8	10	34
Frequent	527	35	91	39	11	14	32

Conclusions: Some 10 per cent of resections were performed by infrequent operators who had the highest operative mortality and poorest survival figures. The results suggest that the workload of an average district general hospital is sufficient to allow a good focus of surgical care for cancer of the oesophagus and cardia.

UGI 002

Effect of surgical specialization on hospital mortality for oesophago–gastric cancer

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Aims: Specialist cancer care is assumed to improve outcome. Although an inverse relationship between surgical experience and hospital mortality has been demonstrated for oesophagectomy, studies are open to criticisms that they have failed to take into account the changing epidemiology of oesophageal and gastric malignancies and the influence of case selection. The aim of this study was to examine the effects of surgical case volume in patients undergoing oesophago–gastric cancer operations on hospital mortality.

Methods: A 1-year prospective cohort study of new patients with oesophageal or gastric cancer in 23 hospital trusts Thirty-day mortalities in operated patients were adjusted for hospital surgical volume, age, albumin levels, ASA grade and resections *versus* other operations. Case volumes were analysed as continuous variables.

Results: Some 1512 new patients with oesophageal or gastric cancer were identified: 726 underwent surgery. The median number of cases operated on per surgeon was 18 (range, 1–42) Overall, 30-day mortalities for oesophageal and gastric operations were 11 per cent and 14 per cent respectively. When mortality was adjusted for the factors noted above, a significant inverse relationship existed between surgeons' case volume and 30-day mortality ($P = 0\ 002$).

Surgeon's surgical volume	Mortality adjusted odds ratio (95% CI)
1	0 965 (0 944–0 987)
10	0 703 (0 560–0 882)
20	0 494 (0 314–0 777)
40	0 244 (0 099–0 604)

Conclusions: More than 50 per cent of oesophago–gastric operations were carried out by surgeons performing less than 20 operations per year. A difference in surgical volume of 20 cases was associated with a halving of the risk of 30-day mortality Oesophago–gastric cancer surgery should take place only in hospitals where surgeons have a high case volume.

UGI 003

Prognostic significance of nodal metastases following subtotal oesophagectomy with two-field lymphadenectomy

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Aims: Although nodal involvement carries a poor prognosis following resection for oesophageal cancer, there are some node-positive patients who are cured by radical surgery. The aim of this study was to evaluate the influence of the number and site of nodal metastases on long-term survival following subtotal oesophagectomy with two-field lymphadenectomy

Methods: From April 1990 to October 1999, 184 patients have undergone primary attempted curative resection with radical upper abdominal and mediastinal nodal clearance under the care of one surgeon. All tumours were confined to the middle or lower third of the oesophagus with a ratio of adenocarcinoma-to-squamous carcinoma of 2:1. Histopathological assessment of the number and sites of nodal metastases were analysed in relation to postoperative survival. Data were excluded from the 4 8 per cent patients suffering in-hospital mortality

Results: The median age of patients discharged from hospital was 64 years (range, 40–77) with a male-to-female ratio of 3:1. The median nodal harvest was 16 (9–57) with 46 per cent of patients (80/175) found to be node-negative and 54 per cent (95/175) node-positive Two- and 5-year survival rates for N0 patients were 86 per cent and 66 per cent, respectively, in contrast to only 33 per cent and 11 per cent for N1 patients (log rank = 65·7; 1 d.f., $P < 0{\cdot}0001$). Multivariate analysis revealed that nodal status was an independent prognostic indicator with the presence of 4 or more positive nodes associated with a significantly worse outcome, irrespective of histological subtype. There were no long-term survivors (longer than 5 years) among those patients having this degree of lymphadenopathy, with a median survival of only 13 months compared with 25 months for those with 1–3 positive nodes (log rank = 12·3; 1 d.f., $P = 0\ 0005$) In those patients with 1–3 positive nodes, over 95 per cent of their nodal metastases were confined to the paraoesophageal, paracardiac and left gastric stations, with no long-term survivors having nodal disease in areas outside these stations

Conclusions: The presence of four or more positive nodes or nodal metastases outside the paraoesophageal, paracardiac or left gastric stations is associated with a particularly grave prognosis If these patients could accurately be identified peroperatively. they might benefit from multimodality therapy or nonsurgical palliation.

UGI 004

Perioperative chemoradiotherapy followed by surgery improves survival for oesophageal squamous cell carcinoma: results of a prospective randomized controlled trial

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Aims: Preoperative chemoradiotherapy followed by surgery (multimodal therapy) leads to an improvement in survival for oesophageal adenocarcinoma. This study examines whether this also pertains to squamous cell carcinoma.

Methods: A prospective randomized trial was carried out from May 1990 to December 1997, comparing multimodal therapy with surgery alone for oesophageal squamous cell carcinoma. The multimodal regime consisted of two courses of 5-fluorouracil (15 mg kg^{-1}) given on days 1–5 and cisplatin (75 mg m^{-2}) on day 7. This course was repeated in week 6. Radiotherapy was given to a total dose of 40 Gy in 15 fractions over 3 weeks, the first week concurrent with the first course of chemotherapy. Patients were followed up in December 1999. Endpoints were morbidity, mortality and survival.

Results: Ninety-eight patients with squamous cell carcinoma of the oesophagus were randomized; 46 to multimodal therapy and 52 to surgical resection alone. Morbidity and hospital mortality were similar between the groups. The complete response rate was 30 per cent based on intention to treat and 35 per cent based on treatment actually received. Survival at 3 years, excluding hospital mortality, was 32 per cent (12/37) for the multimodal limb and 16 per cent (7/43) for surgery alone. The 5-year survival was 36 per cent (9/25) for multimodal therapy and 11 per cent (3/28) for surgery alone. Based on intention to treat, the median survival was 12 months for multimodal therapy *versus* 8 months for surgery ($P = 0.017$). Based on treatment actually received and excluding hospital mortality, the median survival was 27 months for multimodal therapy and 10 months for surgery.

Conclusions: Multimodal therapy confers a significant survival advantage when compared with surgery alone for squamous cell carcinoma of the oesophagus.

UGI 005

Effect of endoscopic ultrasonography on the management of 100 consecutive cases of oesophageal and junctional carcinoma

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Aims: To assess whether the improved staging accuracy offered by endoscopic ultrasonography (EUS) affects surgical decision-making in patients with oesophageal and junctional cancers.

Methods: The case records of 100 consecutive patients referred for EUS, with oesophageal or oesophago–gastric junctional carcinomas, were summarized to contain as much personal and staging information, excluding EUS, as was available for each patient, then blinded. From the summaries, three consultant oesophago–gastric surgeons individually made a management decision based on the information available. The EUS report was added, the summaries rerandomzied and management decision-making repeated. All were asked to score their perceived usefulness of the EUS staging data for each patient (–5 extremely unhelpful, 0 no help; +5 extremely helpful).

Results: EUS staging was performed on 76 male and 24 female patients, median age 68 years (range, 32–88). Some 76 tumours were adenocarcinoma, 22 squamous carcinoma, plus two other carcinomas; 87 per cent of tumours were traversable. EUS resulted in a change of patient management plan in 16, 32 and 18 per cent of the cases respectively. The addition of EUS staging information resulted in an overall increase in agreement by the surgeons, when measured using Cohen's κ analysis (Table). EUS altered the management of four cases by all three surgeons, leading to concordant management in three of the four, and the same management plan by two or the three surgeons in the remaining case. The management of 11 cases was changed by two of the three surgeons with the addition of EUS staging information, leading to concordant management plan in a further three patients. The EUS staging information was deemed useful in the management of 87, 65 and 63 per cent of patients with a median score of 3 (IQR, 2–4), 2 (0–4) and 2 (0–4).

Surgeon	Kappa (pre-EUS)	Agreement	κ (post-EUS)	Agreement
1 *versus* 2	0.42	Moderate	0.62	Good
1 *versus* 3	0.70	Good	0.61	Good
2 *versus* 3	0.47	Moderate	0.62	Good

Conclusions: EUS has been demonstrated to be an extremely useful tool, aiding management decision-making in the majority of oesophageal and junctional cancers, with resultant alteration in management plans leading to improved agreement between surgeons.

UGI 006

Oesophagectomy following iatrogenic perforation of operable oesophageal carcinoma

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Aims: Perforation of operable oesophageal cancer may lead to severe mediastinitis and local dissemination of malignant cells. This study aimed to evaluate the immediate and late clinical outcome after oesophagectomy in such circumstances.

Methods: Between April 1990 and October 1999, 11 patients have undergone subtotal oesophagectomy following instrumental perforation of a malignant stricture. The clinico–pathological characteristics and outcome data of these patients were compared with those of 190 further patients who had undergone elective R0 resection with no history of perforation.

Results: The overall median age was 64 years (range, 40–79) with a male-to-female ratio of 3:1. All tumours were confined to the lower or middle third of the oesophagus. The ratio of adenocarcinoma ($n = 129$) to squamous carcinoma ($n = 72$) was 2.1, with similar distribution in the perforated and nonperforated groups. Some 27 per cent (3/11) of the perforated patients underwent surgery within 24 h, whereas the remaining eight patients experienced a median delay of 52 days (5–148) prior to resection. Outcome data are shown in the table.

	Perforation ($n = 11$)	No perforation ($n = 190$)	*P* value
Median blood loss	1000 mL	800 mL	NS
Median operative time	210 min	245 min	NS
Median lymph node yield	9.5	16.5	0.031
Anastomotic leak rate	0%	2.6%	NS
Mortality	0%	4.7%	NS
Median survival	9 months	25 months	0.0266

Overall 1-year survival in the perforated group was 40 per cent, with the longest survivor alive at 18 months. In contrast, 1- and 2-year survival in the nonperforated group were significantly better at 78 per cent and 52 per cent, respectively, with this benefit still apparent after stratification according to stage.

Conclusions: Early or delayed oesophageal resection after iatrogenic perforation is safe with a lower morbidity than normal elective procedures. While early surgery may be indicated for potentially life-threatening complications, overall survival is so poor that such perforations may be better managed conservatively with subsequent nonsurgical tumour palliation.

Moynihan 001

Can a platelet-activating factor antagonist ameliorate the reperfusion-associated sequelae of femoro-popliteal bypass?

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Aims: Platelet-activating factor (PAF) release during ischaemia–reperfusion injury (IRI) promotes potentially detrimental neutrophil recruitment, proinflammatory mediator production, and platelet aggregation. PAF antagonists, such as lexipafant, have reduced IRI-related tissue oedema and necrosis in experimental models, although, to date, few clinical studies have examined the therapeutic use of such single-mediator antagonists in IRI.
Methods: This double-blind randomized study evaluated lexipafant (200 mg IV over 48 h), $n=20$ (L) *versus* placebo, $n=20$ (P) on systemic (SV) and femoral (FV) venous mediator levels (IL-6, IL-8, E-selectin, TxA$_2$, TNFα at 0 h, 4 h, 24 h, 72 h postreperfusion) and postoperative limb swelling (calf circumference and volume) in patients undergoing femoro-popliteal bypass surgery.
Results: FV and SV IL-6 increased in both groups and peaked at 24 h ($P<0{\cdot}001$), the FV level was significantly higher in L *versus* P (SV 92·1 pg mL^{-1} *versus* 84·7 pg mL^{-1}; FV: 235·7 pg mL^{-1} *versus* 123·6 pg mL^{-1}, $P=0{\cdot}005$). IL-8 and TxA$_2$ were also similarly elevated but the levels were not significantly different in L *versus* P (SV 24 h IL-8 25·3 pg mL^{-1} *versus* 27·7 pg mL^{-1}, TxA$_2$ 83·5 pg mL^{-1} *versus* 127·7 pg mL^{-1}, FV 24 h IL-8 25·4 pg mL^{-1} *versus* 23·9 pg mL^{-1}, TxA$_2$ 116·9 pg mL^{-1} *versus* 122·9 pg mL^{-1}). No differences occurred in SV and FV samples at the other time points. E-selectin and TNFα levels did not significantly change from baseline at any sampled points. Further, lexipafant did not significantly reduce ipsilateral limb volume (6 days. +13 per cent *versus* +16 per cent, 42 days +5 per cent *versus* +11 per cent) or calf circumference (6 days +1·5 cm *versus* +2·5 cm, 42 days: +1·0 cm *versus* +1·7 cm) *versus* controls.
Conclusions: Increased local and systemic proinflammatory mediator levels, with development of limb oedema following lower-limb revascularization are consistent with IRI; however, neither was significantly influenced by lexipafant. This study elegantly demonstrates the pragmatic problems associated with the use of single-mediator antagonists in IRI.

Moynihan 002

Randomized trial of Prograf *versus* Neoral in cadaveric renal transplantation: 189 patients with a minimum 1-year follow-up

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Aims: Several studies have confirmed the efficacy of tacrolimus (Prograf) over cyclosporin (Sandimmun) in cadaveric renal transplantation. However, none has compared it with the new microemulsion preparation Neoral.
Methods: Between 1996 and 1998, 179 patients were randomized to either Prograf- ($n=90$) or Neoral- ($n=89$) based triple therapy. Initial doses were 0·2 mg kg^{-1} day^{-1} and 8 mg kg^{-1} day^{-1} respectively. Patients also received azathioprine 1·5 mg kg^{-1} day^{-1} and prednisolone 20 mg day^{-1}. Steroid doses were tapered to 5 mg by 12 weeks and then withdrawn unless the patient had been treated for acute rejection.

Results:

	Prograf ($n=90$)	Neoral ($n=89$)	Analysis
3-year actuarial graft survival rate	88	76	$P<0{\cdot}05$
3-year cumulative death rate	4·4	7·9	NS
3-year cumulative graft loss rate	4·4	9·0	NS
Median 1-year serum creatinine (μmol L^{-1})	129	153	$P<0{\cdot}05$
Median 2-year serum creatinine (μmol L^{-1})	129	157	$P<0{\cdot}05$
Median 3-year serum creatinine (μmol L^{-1})	132	156	$P<0{\cdot}05$
Acute rejection rate	23	42	$P<0{\cdot}05$
Requirement for antilymphocyte agents	2·3	9·3	NS
Conversion to alternative baseline	2·3	11·6	NS
Conversion from azathioprine to MMF	9·1	16·3	NS

Conclusions: Short-term patient and graft outcomes are superior in patients receiving tacrolimus. Continuation of this study will determine if these early benefits translate into improved long-term results.

Moynihan 003

Insulin-like growth factor (IGF)-I and risk of colorectal neoplasia

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Aims: Circulating insulin-like growth factor (IGF)-I and its main binding protein (IGFBP-3), are age-dependent and demonstrate wide interindividual variation within a population. This study aims to investigate the hypothesis that high normal range IGF-I and low normal range IGFBP-3 predict for colorectal cancer risk in an age-controlled group screened for colonoscopy.
Methods: To investigate the stages of colorectal carcinogenesis, IGF-I and IGFBP-3 were measured using radioimmunoassays in four groups: (i) individuals with normal colonoscopy ($n=37$), (ii) low-risk adenomas (<1 cm, tubular histology) indicating tumour initiation ($n=16$), (iii) high-risk adenomas (≥1 cm, tubulovillous histology, severe dysplasia, multiplicity) indicating adenoma progression ($n=27$), and (iv) adenocarcinomas ($n=28$). Samples were prospectively collected and all patients were aged 50–65 years with complete colonoscopy to the caecum. Patients with advanced cancer and malnutrition were excluded. Estimates of relative risk were calculated using multiple logistic regression and odds ratios.
Results: Mean serum IGF-I levels were elevated in patients with high-risk adenomas (mean ± s.e., 189 ± 12 μg L^{-1}) and adenocarcinomas (197 ± 11 μg L^{-1}) compared with patients with low-risk adenomas (167 ± 12 μg L^{-1}) and normal colonoscopy (163 ± 9 μg L^{-1}, 1-ANOVA, $P=0{\cdot}09$). Controlling for IGFBP-3, relative to individuals in the low-tertile of IGF-I, those in the high-tertile were at increased risk of developing high-risk adenomas and carcinomas combined (relative risk, RR=2·18, 95% CI=0·71–6·8). Controlling for IGF-I, the risk for individuals in the low-tertile of IGFBP-3 was equivocal (RR=1·06; 95% CI=0·41–2·75). However, the interaction of low IGF-I and high IGFBP-3 was associated with a low risk for high-risk adenomas and adenocarcinoma combined (RR=0·28; 95% CI=0·10–1·5).
Conclusions: This study has demonstrated that circulating IGF-I is predictive for colorectal cancer risk, specifically the progression from low-risk adenoma to high-risk adenoma. These findings support epidemiological data demonstrating similar associations in other cancers, and point to novel biological mechanisms in colorectal carcinogenesis.

Moynihan 004

IL-10 knockout model of colitis: new similarities to human inflammatory bowel disease

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Aims: Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine Disruption of the IL-10 gene in C57/B6 mice results in chronic enterocolitis in the presence of intestinal bacteria. This study investigated the gut mucosal barrier function sequentially during the development of colitis in IL-10 knockout mouse raised in conventional conditions.
Methods: Animals were bred and weaned in specific pathogen free conditions and then transferred to a conventional environment at 4 weeks of age. Animals ($n=5$–6 per group) were evaluated at 6, 8, 10, 12, 14 and 15 weeks of age Twenty-four hours prior to completion of the experiment, mice received radiolabelled polyethylene glycol by gavage and were housed in a metabolic cage Urine was collected for 24 h to assess gut permeability. Animals were anaesthetized and blood taken by cardiac puncture for EndoCAb measurement; colons were harvested for histological inflammation scoring (HIS)
Results: Expressed as mean ± s e m

Age (weeks)	HIS	Permeability	EndoCAb
6	0·33 ± 0·21	0·22 ± 0·05	75·6 ± 2·17
8	1·83 ± 0·48	0·13 ± 0·02	82·1 ± 8·80
10	3 ± 0·45	0·69 ± 0·29	82·3 ± 5·82
12	7·17 ± 1·19	0·76 ± 0·17	91·6 ± 4·87
14	4·75 ± 1·80	1·17 ± 0·44	79·2 ± 5.14
15	6·5 ± 1·57	1·11 ± 0·38	118·4 ± 16·6

Permeability was normal in 6- and 8-week-old animals, suggesting an intact gut barrier Permeability then increased in a parabolic fashion before plateauing at 14 weeks Permeability correlated with the HIS ($r^2=0·814$, $P<0·001$) and IgG EndoCAb ($r^2=0·406$; $P=0·032$). The HIS correlated positively with IgG EndoCAb ($r^2=0·548$; $P=0·03$).
Conclusions: IL-10 knockout mice from the C57/B6 background develop colitis between 8 and 10 weeks of age with associated disturbance in gut mucosal barrier function as measured by increased permeability and endotoxaemia. The colitis found in the IL-10 knockout mouse shares these pathological and physiological features of human IBD and is therefore ideal for therapeutic trials.

Moynihan 005

Hypertonic saline attenuates end-organ damage in an *in vivo* model of acute pancreatitis

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Aims: Hypertonic saline (HTS) has previously been noted to exert an immunomodulatory effect, reducing neutrophil activation. The aim of the present study was to elucidate the effect of hypertonic resuscitation on the development of end-organ damage in an animal model of pancreatitis, a disease process characterized by a systemic inflammatory response and an ensuing neutrophil-mediated lung injury
Methods: Pancreatitis was induced in 16 Sprague–Dawley rats by intraperitoneal injection of 20 per cent L-arginine (500 mg 100 g^{-1} body weight). In eight rats, resuscitation was performed at 24 and 48 h with a 2 ml kg^{-1} intravenous bolus of HTS (7·5 per cent NaCl), and a further 14 animals received a 2 ml kg^{-1} bolus of normal saline (NS, 0·9 per cent NaCl) at the same time points Serum amylase was assessed at 24 and 72 h, and systemic neutrophils were measured at 72 h. Myeloperoxidase activity (MPO) was employed as a marker of pulmonary neutrophil infiltration, and pulmonary endothelial leak was assessed using bronchoalveolar lavage (BAL) protein content, in addition to wet/dry lung weight ratios In order to validate our results, representative histological sections of lung and pancreas were blindly assessed by a pathologist
Results: HTS animals evinced less lung and pancreatic damage than those resuscitated with normal saline Pulmonary endothelial permeability in HTS animals was significantly decreased ($P=0·04$). Histopathological pancreatic injury scores were significantly reduced ($P=0·01$), and lung injury scores were correspondingly diminished ($P=0·02$) NS resuscitated rats exhibited a significantly lower peripheral neutrophil count than HTS animals (mean 6·38 *versus* 7·74, $P=0·04$) In addition, pulmonary neutrophil infiltration was also attenuated in the HTS treated group

	Lung wet/dry ratio	Pancreatic injury	Lung injury
HTS group	5·69 ± 1·29	1·00 ± 0·0	1·63 ± 1·50
NS group	8·22 ± 2·87	5·12 ± 4·15	4·75 ± 3·15
P value	0·04	0·01	0·02

Data mean ± s d, statistics Student's *t*-test

Conclusions: This study demonstrates that HTS resuscitation results in a significant attenuation of end-organ injury following a systemic inflammatory response subsequent to severe pancreatitis.

Moynihan 006

Mammaglobin and CEA expression can increase the detection of nodal micrometastases with breast cancer patients

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Aims: To assess whether (i) RT-PCR is superior to routine histology for the detection of axillary metastases in breast cancer patients; (ii) mammaglobin and CEA genes are suitable markers of breast cancer micrometastases
Methods: Twenty-one consecutive patients with proven carcinoma of the breast underwent tumour excision, sentinel node biopsy and clearance Nodes were isolated from the axillary fat and bisected; half was sent for routine histological examination and half underwent RNA extraction and RT-PCR to look for expression of the mammaglobin and CEA genes.
Results: Some 161 nodes from 21 patients were sent for both histology and RT-PCR; 32 (20 per cent) nodes from seven (33 per cent) patients were histologically positive, 23 (14 per cent) nodes from six (28 per cent) patients expressed CEA; 39 (24 per cent) nodes from eight (38 per cent) patients expressed mammaglobin; 40 (25 per cent) nodes from nine (42 per cent) patients expressed one or both markers. The difference between routine histology and PCR for both genes is statistically significant ($P=0·02$)
Conclusions: (i) RT-PCR is superior to routine histology for the detection of axillary metastases. (ii) Mammaglobin and CEA comprise a sensitive and highly specific marker panel.

UGI 007

A study to determine optimum timing of bariatric surgery following intragastric balloon placement

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Aims: To monitor weight loss and determine optimum removal time of intragastric balloons in a group of patients before bariatric surgery.
Methods: Saline-filled intragastric balloon insertion is a therapeutic option in the management of patients with morbid obesity. Patients often regain weight once the balloon is removed and bariatric surgery is required, which would be best performed once maximum weight loss with the balloon has been achieved The optimum timing of conversion from balloon to surgery is not known. Thirty-eight consecutive patients who were able to tolerate balloon therapy were studied. The M.F was 13.25 with a median age of 41 years (range, 25–66), mean BMI of 53 5 kg m^{-2} (range, 31·5–86·5) and a median weight of 137·6 kg (range, 86 4–223·0) A BioEnterics intragastric balloon was inserted and inflated with 750 mL normal saline Patients were placed on a 800 kcal diet and weight and balloon status monitored. Balloon volume was determined by ultrasound.
Results: Weight loss was greatest during the first 4–8 weeks following placement, with a mean loss of 6 kg week^{-1} (±4·4 s.d.). By 12 weeks, the rate of loss had fallen to a mean of 1.5 kg week^{-1} (±1·8 s.d), and this was maintained until 35 weeks. Nine patients reported no side effects, 19 had up to 3 days of nausea and vomiting, five had symptomatic reflux. Twenty-one balloons either spontaneously deflated or were found to be missing on ultrasound examination; the median life of these balloons was 31·5 weeks (range, 1–58)
Conclusions: Intragastric balloon placement is a simple and effective short-term means for achieving weight loss in morbidly obese people for whom bariatric surgery is planned. Our data suggest that the optimum time for surgery is 20–24 weeks after insertion of an intragastric balloon in order to achieve maximum weight loss and minimize the risk of balloon failure.

UGI 008

Chronic dysphagia following laparoscopic fundoplication

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Aims: Many surgeons practice tailored laparoscopic antireflux surgery in an attempt to prevent postoperative dysphagia. The aim of this study was to determine the effect of 360° fundoplication (Nissen) or 270° fundoplication (Toupet), and the influence of abnormal oesophageal peristalsis, upon postoperative dysphagia
Methods: Prospective cohort study from three tertiary referral centres, with 1-year follow-up, using dysphagia as the main outcome variable. DeMeester dysphagia scores (0–3) were undertaken before laparoscopic fundoplication and 1-year postoperatively Preoperative oesophageal manometry was performed on all patients.
Results: Some 761 patients underwent Nissen and 85 patients underwent Toupet fundoplications. Only 2 per cent reported severe postoperative dysphagia. Overall, there was no significant change in dysphagia from pre- to postoperatively in the Toupet group. However, after Nissen fundoplication, there was a significant improvement in dysphagia ($P=0\ 02$) There was a significant selection bias towards the Toupet operation for patients with abnormal oesophageal motility ($P<0\ 001$). A subgroup analysis for patients whose oesophageal manometry was stratified as normal indicated there was a significant improvement in dysphagia after Nissen fundoplication ($P=0{\cdot}02$), and there was no significant change following Toupet fundoplication. There was no significant change in dysphagia following either fundoplication among other subgroups, whose oesophageal manometry was stratified as nonspecific motor disorder, low-amplitude peristalsis, or aperistalsis.
Conclusions: A tailored approach to the degree of fundoplication is unnecessary, as patients with dysmotility suffer no more dysphagia after a full laparoscopic Nissen fundoplication than those who have a partial Toupet wrap.

UGI 009

Nonobstructive dysphagia in patients with gastro-oesophageal reflux disease (GORD) – is manometry helpful?

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Aims: About 30 per cent of GORD patients without strictures experience dysphagia. It has been attributed to poor oesophageal motility, leading to the belief that such patients are unsuited to standard antireflux surgery The aim was to compare standard (SM), provocation (bread swallow) (PM) and ambulatory manometry (AM) in the assessment of nonobstructive dysphagia in patients with GORD.
Methods: Sixty healthy controls and 51 GORD patients were studied All underwent 24-h pH monitoring with SM, PM and AM. Validated dysphagia scores were measured and dysphagia during manometry assessed. Poor motility was defined using established criteria for each type of manometric study
Results: All controls had normal dysphagia scores, 24-h pH profiles and manometry studies. Poor motility was present in 31 SM, 34 PM and 22 AM patients. Dysphagia was present in 7/20 patients with normal motility on SM compared with 13/31 with poor motility on SM ($P=0{\cdot}91$), 6/17 with normal motility on PM compared with 14/34 with poor motility on PM ($P=0{\cdot}82$) and 12/29 with normal motility on AM compared with 8 22 with poor motility on AM ($P=0{\cdot}62$) (Pearson χ^2 test).
Conclusions: There was no correlation between dysphagia and poor motility with any manometric test. Manometry cannot identify a group of GORD patients who are unsuited to standard antireflux surgery

UGI 010

Gastric cancer – a curable disease for only a minority of patients in Britain

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Aims: Vigorous efforts aimed at early diagnosis, together with the adoption of radical Japanese surgical techniques are factors cited for the improving survival following surgery for gastric cancer reported in selected centres. The aim of this study was to audit the results of attempted curative gastrectomy in a UK unit adopting this approach.
Methods: A prospective audit of a consecutive series of patients undergoing R0 radical gastrectomy for primary gastric adenocarcinoma between 1 March 1989 and 31 October 1999.
Results: Of 415 patients treated over this time period, 160 (39 per cent) have undergone potentially curative resection with a median age of 68 (31–88) years and a male-to-female ratio of 2:1. Tumour distribution was antrum ($n=43$), body ($n=33$), cardia/fundus ($n=74$) and stump or stoma ($n=10$). Some 107 total gastrectomies, 43 subtotal gastrectomies and 10 completion gastrectomies, were performed with 52 per cent of patients (82/160) undergoing a D2 or D3 nodal clearance and the remainder having an extended D1 clearance Pancreatico-splenectomy was performed in 13 patients and isolated splenectomy in a further 21. Thirty-day and in-hospital mortality were 2·5 per cent and 3·8 per cent, respectively, with major

morbidity occurring in a further 26 per cent of patients. Disease-specific survival figures for the 154 patients discharged from hospital at 1, 2 and 5 years according to TNM stage (UICC 5th edition) are shown in the table

	n	1-year	2-year	5-year	Median
Stage 1a/b	61	100%	96%	93%	>60 months
Stage 2	35	91%	77%	45%	48 months
Stage 3a/b	46	73%	47%	10%	21 months
Stage 4	12	36%	0%	0%	11 months

Log rank=89 92, 3 d f , *P*<0 0001

Conclusions: While a high proportion of early gastric cancers can be detected and treated safely with excellent long-term outcome, the prognosis following radical gastrectomy for more advanced disease is poor. Radical surgery alone continues to fail the majority of patients with operable gastric cancer in our unit

UGI 011

The effect of probiotics on septic morbidity and mortality in critically ill patients

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Aims: Impairment of gut barrier function and consequent bacterial translocation (BT) may be important in the pathophysiology of septic morbidity and multiple-organ failure in the critically ill The aim of this study was to assess the effect of the probiotic *Lactobacillus plantarum 299v* on the incidence of septic complications and mortality in a series of critically ill patients.

Methods: In this prospective randomized controlled study, intensive care unit (ICU) patients were randomized to receive an oral preparation containing *L plantarum 299v* (*ProViva*) in addition to conventional therapy (treatment group) or conventional therapy alone (control group) All septic morbidity, including causative organisms, and overall mortality was recorded.

Results: A total of 90 patients were entered into the study.

	ProViva group (*n*=45)	Control group (*n*=45)	*P* value
M F ratio	31 14	24 21	–
Median age (IQR)	1 year (66–77)	71 years (61–77)	–
Incidence of septic morbidity	38%	38%	>0 05, NS
No of complications per patient	0 56	0 53	>0 05, NS
Mortality rate	38%	36%	>0 05, NS

Enteric bacteria were implicated in 37/49 (76 per cent) of all septic complications

Conclusions: The results of this study do not show any evidence of benefit of the probiotic *L plantarum 299v* in terms of septic morbidity or mortality in critically ill patients.

A UGI 012

Roux-en-Y gastric bypass: a safe and effective operation in morbidly obese and superobese patients

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Aims: To describe the early results of Roux-en-Y gastric bypass in morbidly obese and superobese patients, and to evaluate patient satisfaction with the operation.

Methods: Between August 1995 and June 1998, 101 patients (89 females) with a median age of 39 years (range, 24–61) underwent Roux-en-Y gastric bypass for morbid and superobesity. The median preoperative body mass index (BMI) was 51 (range, 35–90) Comorbid factors included hypertension (40 per cent of patients), diabetes mellitus (5 per cent), osteoarthritis (76 per cent), sleep apnoea (17 per cent). Ten patients had previously undergone antiobesity surgery elsewhere The median duration of follow-up was 24 months. Questionnaires were sent at 12 months postoperatively to examine changes in comorbidity, symptomatic status and patient satisfaction with the operation.

Results: One patient had a concomitant splenectomy for iatrogenic injury (intraoperative complications 1 per cent). Postoperative complications included chest infection (8 per cent), wound infection (20 per cent) and deep vein thrombosis (1 per cent). One patient who suffered with sleep apnoea died on the second postoperative day following a respiratory arrest (mortality, 1 per cent) Median hospital stay was 5 days Late complications included staple line disruption (1 per cent), stomal ulceration (2 per cent), incisional hernia (6 per cent) and pulmonary embolism (1 per cent) The median reduction in BMI was 26 per cent at 6 months (*P*<0·0001, Wilcoxon signed rank test), 40 per cent at 12 months, and 38 5 per cent at 24 months A significant improvement in comorbidity was observed and included improvements in hypertension in 79 per cent, diabetes in 80 per cent, painful joints in 87 per cent, snoring in 83 per cent, urine incontinence in 65 per cent and depression in 82 per cent of affected patients. Of the 88 patients who completed questionnaires, 86 per cent were very satisfied, 9·5 per cent were satisfied, 2 3 per cent were indifferent and 2 3 per cent were unhappy with the results of surgery. When asked if they would recommend the operation to someone else, 96·5 per cent of patients answered 'yes', while 2 5 per cent answered 'no'

Conclusions: Roux-en-Y gastric bypass is a safe and effective operation for morbid obesity, results in a marked and rapid improvement in health status and achieves high patient satisfaction.

General 001

Cigarette smoking is an aetiological factor in hidradenitis suppurativa

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Aims: Hidradenitis suppurativa (HAS) is a chronic relapsing inflammatory disease of apocrine glands, which often requires extensive and recurrent surgical excision. The aim of this study was to determine the relationship between smoking and HAS.
Methods: All patients admitted for excision of HAS between 1990 and 1998 were identified HAS was confirmed by pathological examination of the excised tissue. Patients' smoking habits and use of oral contraceptives were recorded from the medical history taken at the time of first admission Bacteriology results were those taken from swab cultures from the wound preoperatively Recurrent disease was defined as disease following previous excision or in a new site. An age- and sex-matched control admitted within 1 year of the index patient was selected from patients attending for surgery for varicose veins ($n=29$), hernia repair ($n=21$), cholecystectomy ($n=15$) or skin excisional biopsy ($n=27$). Analysis was performed using χ^2 test.
Results: We identified 92 patients with HAS, over the 9-year period, of which 65 (71 per cent) were female and 27 (29 per cent) male. Of these, 84 (91 per cent) were smokers and only eight (9 per cent) were nonsmokers. In addition, 12 (18 per cent) women took an oral contraceptive In the control group, only 34 (37 per cent) were smokers and, of the women, 14 (22 per cent) took an oral contraceptive. Mean age for both groups was 36·6 years. There were 21 patients (23 per cent) with a positive swab culture, of which 20 (95 per cent) were smokers. *Staph aureus* was the commonest pathogen cultured Recurrent disease was seen in 31 patients (34 per cent), of which 28 (90 per cent) were heavy smokers. Of all factors considered, smoking was the only significant risk factor for HAS, with a relative risk factor value of 2·47 (95% CI 1·9–3·25). $\chi^2=57$ ($P<0{\cdot}001$)
Conclusions: Sufferers of hidradenitis are more likely to be female smokers. Recurrent disease and bacterial infection is common among heavy smokers No association was seen with the oral contraceptive pill.

General 002

Preemptive analgesia by local anaesthetic infiltration: a prospective double-blind randomized placebo-controlled trial

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Aims: The efficacy of preemptive local anaesthetic (PEA) infiltration is unproven.
Methods: Some 107 patients were included (68 males, 39 females; 21 appendicectomy, 32 hernia repair, 54 laparoscopic cholecystectomy/fundoplication). Forty-nine patients were placed in the control group and 58 in the treatment group by simple unblocked randomization. Exclusion criteria were contraindications to use of bupivacaine, nonsteroidal anti-inflammatory drugs (NSAIDs) or morphine (postoperative analgesia was limited to the latter two) Following randomization, patients received either 10 mL of 0·5 per cent bupivacaine or 10 mL 0·9 per cent saline by local infiltration of the proposed incision site (hernia repair patients were infiltrated as for repair under local anaesthetic) A standard questionnaire was completed by the patient, which included visual and analogue pain scores and satisfaction rating (with postoperative analgesia) A strict record of patient analgesic use was conducted
Results: The table demonstrates the pain scores of patients for the included time points (ANOVA for repeated measures and least-square means and associated standard error $P<0{\cdot}0001$*)

	1 h	3 h	12 h	24 h
Bupivacaine	2·81 ± 0·25*	3·56 ± 0·25*	3·12 ± 0·25*	2·04 ± 0·25*
Placebo	6·66 ± 0·26	6·48 ± 0·26	5·80 ± 0·26	3·49 ± 0·26

There was a significantly lower pain score in the treatment group ($P=0{\cdot}0001$), which was maintained at all measured time points over a 24-h period, with male patients reporting lower pain scores ($P=0{\cdot}02$). Analgesic requirements were lower in the PEA group, both for NSAID ($P=0{\cdot}005$) and opiates ($P=0{\cdot}0001$). This was true for all surgical procedures. Patient satisfaction was significantly better in the PEA group ($P=0{\cdot}0001$)
Conclusions: Preemptive local anaesthetic infiltration with bupivacaine should be the standard practice for patients undergoing laparoscopic surgery, conventional appendicectomy and inguinal hernia repair

General 003

Should contralateral incidental defects found on laparoscopic repair of groin hernia be repaired? Early results of a randomized controlled trial

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Aims: Controversy exists about the routine repair of contralateral incidental defects identified during laparoscopic TAPP repair of groin hernia. Its reported incidence is 10–25 per cent and we present the early results of a prospective randomized control study designed to follow the clinical behaviour of these defects
Methods: Thirty-seven male patients who were found to have incidental defects on the contralateral side during laparoscopic TAPP repair of groin hernia were prospectively randomized into two categories. In 16 patients (controls), the defects were repaired simultaneously and, in the remaining 21 patients (trial group), operative repair was not done. Follow-up was done subsequently by an independent clinician to detect any adverse symptoms in the control patients and any clinically demonstrable hernias in the trial group.
Results: The median follow-up periods for the control and trial groups were 15 and 12 months respectively During this time, none of the control group had any untoward symptoms, while six patients in the trial (28·6 per cent) developed clinically demonstrable hernias.
Conclusions: This study has demonstrated that, despite a short follow-up period, a significant proportion of incidental defects progress to a symptomatic hernia if left untreated Hence, their simultaneous repair may be justified on the grounds that it reduces the number of operations, hospital visits and cost to the NHS, and is of major benefit to the patient.

General 004

Results of inguinal canal repair in athletes with groin disruptions

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Aims: To evaluate the role of surgical exploration and repair of the inguinal canal in athletes with suspected sports hernia
Methods: Thirty-five athletes with suspected sports hernia underwent surgical exploration and inguinal hernia repair between 1994 and 1999. After 6 months, all athletes were sent questionnaires to assess the improvement in their pain scores (using analogue pain scores), return to sport, recurrence of the symptoms and overall result of their surgery

Results: Operative findings revealed a tear in external oblique aponeurosis with or without a significant posterior bulge ($n=20$), only a significant posterior bulge ($n=10$), tear in the conjoint tendon with dilated superficial ring ($n=3$), small direct hernial sac ($n=1$) and lipoma of the spermatic cord ($n=1$). Surgery consisted of repair of external oblique tear (when present) and prolene darn or lichtenstein mesh repair of the posterior inguinal canal. Twenty-seven patients replied to the questionnaire, giving a response rate of 78 per cent. Of these, 25 patients (92 per cent, 95% CI 83–100) had returned to normal athletic activities to pre-injury level. There was a marked improvement in their level of pain (Wilcoxon signed ranks test, $P<0{\cdot}001$). Eleven patients (41 per cent) indicated the results were excellent, 11 (41 per cent) as good and five (18 per cent) as improved. Six patients complained of occasional discomfort related to the scar. Three patients complained of recurrence of their symptoms 4–5 months following strenuous exercise.
Conclusions: Athletes with suspected sports hernia should be considered for routine inguinal hernia surgery. However, it is important to offer a structured rehabilitation programme to these patients to maximize the benefit.

General 005

Prospective randomized trial of laparoscopic (transabdominal preperitoneal, TAPP) *versus* open (Lichtenstein) inguinal hernia repair for bilateral and recurrent inguinal hernia

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Aims: To compare laparoscopic herniplasty against open mesh (OM) repair in patients with bilateral (BIH) or recurrent (RIH) inguinal hernia.
Methods: From September 1997 to November 1999, 90 patients with 56 recurrent and 34 bilateral inguinal hernias were randomized to TAPP (45 patients) or OM (45 patients) repair. Operating time, complications, pain, hospital stay, resumption of normal activity and work, quality of life and recurrences were recorded.
Results: Pretreatment age, type of hernia, duration of hernia and well-being score were not significantly different in both groups. Mean operating time was 45·5 min for TAPP and 60·4 min for OM ($P=0{\cdot}004$). Visual analogue pain score was 2·4 in the TAPP group as compared with 4·8 in the OM group ($P<0{\cdot}001$). Mean hospital stay was 1·4 days in the TAPP group and 1·8 days in the OM group ($P=0{\cdot}495$). Patients were mobile without pain after a mean of 6·8 days in the TAPP group as compared with 16·4 days in the OM group ($P=0{\cdot}004$). Patients resumed work after a mean of 17·7 days in the TAPP group and 40·0 days in the OM group ($P=0{\cdot}002$). Three months after surgery, mean quality of life score improved by 2·2 points in the TAPP group and 3·0 points in the OM group ($P=0{\cdot}699$). Most complications were minor other than two port hole complications in the TAPP group and one CVA in the OM group. There were four recurrences in the laparoscopic group.
Conclusions: TAPP repair for recurrent and bilateral inguinal hernia gives reduced postoperative pain and allows a shorter convalescence period, with earlier return to work. In addition, operating time was significantly shorter. Length of hospital stay, complications and quality of life scores are similar for both methods.

General 006

Hernia repair in Scotland

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Aims: The use of mesh in groin hernia repair has dramatically changed the way this common operation is performed. The aim of this study was to examine methods of hernia repair and outcome of patients undergoing this operation in Scotland.
Methods: Data were gathered on all adults undergoing groin hernia repair in the National Health Service in Scotland over a 1-year period (April 1998–March 1999).
Results: Some 5649 underwent hernia repair over the 1-year period. Information was obtained on 5506 (97·5 per cent) of these. Patients were on the waiting list a median of 87 days before their operation, while 5 per cent were emergency admissions. Some 85 per cent of patients had an open mesh repair, while 4 per cent had a laparoscopic repair. Most were performed (85 per cent) using general anaesthesia on an inpatient basis (78·5 per cent). Almost 8 per cent of operations were for repair of a recurrent hernia. Although 90 per cent of patients had some form of mesh repair, there was a significant ($P<0{\cdot}01$) trend not to use mesh in people under 30-years-old. Significant trends were also noted for use of a laparoscopic or open preperitoneal repair for bilateral and recurrent hernias. Postoperative mortality was 0·1 per cent and potentially serious intraoperative complications were rare, although the latter was significantly ($P<0{\cdot}001$) more likely to be associated with laparoscopic repair or repair of a femoral hernia. Wound complications such as haematoma (7 per cent) or infection (8 per cent) were common, with one in 10 patients requiring a district nurse to attend their wound.
Conclusions: While this study highlights the satisfactory short-term outcome from groin hernia repair in Scotland, significant change to improve outcome can be instituted on the basis of the information obtained.

Breast 001

Do GPs overrefer to breast clinics? A randomized trial

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Aims: Two editions of GP referral guidelines have been published but it is unknown whether these are effective.
Methods: This randomized trial studied GP practices which were formally educated on the guidelines' algorithms for breast pain and lump (intervention practices) compared with GPs who were simply sent the guidelines through the post (control)
Results: Some 1022 women in 34 practices were studied and 497 were randomized to the intervention practices and 462 to the controls The mean presentations per GP were seven per year (lower than the literature suggests) and the overall referral rate was 55 per cent of all symptomatic women (78 per cent for lump and 25 per cent for mastalgia). The intervention practices had significantly higher concordance rates with the published guidelines (12 per cent higher for lump and 23 per cent higher for lumpiness compared with control practices). Patients in the intervention practices fared better in terms of health outcomes measured by SF-36 and Cardiff Breast Scales However, costs were higher in the intervention practices (£548 higher for lump and £115 higher for lumpiness), although the QALY gains were similar in both groups.
Conclusions: It is possible to increase concordance with GP referral guidelines but at increased cost Practices that conform better to the guidelines do improve the health outcomes of their patients

Breast 002

Should screening mammography be offered for women starting HRT?

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Aims: There is a lack of clear guidelines on screening mammography for women on or starting hormone replacement treatment (HRT) This study was carried out to determine if screening mammography is effective in women starting HRT
Methods: Data for this audit have been collected prospectively from 1 April 1991 to 31 March 1998. Patients commencing HRT referred by their GPs have been offered two view screening mammography. Two-yearly follow-up mammography was also offered if they continued on HRT. All patients with mammographic abnormalities were recalled and managed according to the protocols of the National Breast Screening Programme but were seen on the symptomatic side
Results: The following results were obtained. (1) Over the 7-year study period, a total of 5436 women were screened and 31 cancers (26 invasive and five DCIS) detected (rate per 1000 women screened = 5·7). Ages ranged from 42 to 75 years. (2) Fifteen patients with cancers were outside the NHS screening age, and 15 had refused mammography under the NHS screening programme. (3) Some 1916 patients have been on follow-up with 2-yearly mammograms, resulting in the identification of four additional cancers (4) The overall benign malignant diagnostic biopsy ratio was 1·1 (5) Mean size of lesions detected was 15 mm (6) Fifteen cancers picked up were grade 1 and 22 were ER positive (70 per cent) (7) Nineteen patients underwent breast-conserving surgery and 24 were found to be node negative
Conclusions: Breast cancer, its early detection and possible influences of HRT have emerged as important public health issues In our study, pre-HRT mammograms detected a considerable number of breast cancers and should be investigated further.

Breast 003

Breast clinic referrals: does it matter who grades the letters for urgency?

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Aims: Referral letters from GPs have been graded for urgency by the consultant and registrar since 1992, to allocate suitable clinic appointments. This study compares grading by two consultants (C) and one GP in 1999 with a similar period in 1993.
Methods: Between April and September, GP letters were graded urgent (U) (likely cancer), soon (S) (unlikely but possible cancer), routine (R) (other problem) The consultants followed their usual practice and GP saw the letters without knowledge of the previous decision. The breast cancers (Cas) in each assessor's group and the 1993 results were all compared
Results:

	U			S			R		
	No	Ca	% Ca	No	Ca	% Ca	No	Ca	% Ca
C	217	59	27	360	11	3	316	2	0·6
GP	209	66	32	320	5	1·5	304	0	0
1993	93	41	44	186	11	6	216	4	2

All assessors performed similarly (χ^2 NS) The number of referrals increased from 496 in 1993 to 883 in 1999 (78 per cent increase). The proportion with cancer dropped from 11 per cent to 9 per cent. Only 24 out of 69 GP referrals with Ca fulfilled the 14-day rule referral criteria (directive HSC242/9A).
Conclusions: Any experienced doctor may safely interpret the information in a breast clinic letter. Pressure on fast-track clinics could be reduced by setting up additional clinics staffed by nursing and nonconsultant staff for routine referrals

Breast 004

Referral pathways from primary care in the light of the new NHS breast cancer waiting-times target

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Aims: The notion that earlier diagnosis and treatment of breast cancer results in improved long-term survival has resulted in new government directives, where 'urgent suspected breast cancer' referrals are seen in specialist breast clinics within 2 weeks of the referral being received from the GP; agreed criteria exist as to what constitutes grounds for urgent referral and GPs are now urged to use standardized referral formats (*proformas*) to ensure efficient fast-tracking The aim of this study was to look at the appropriateness of GP referrals to the fast-track breast clinics over the 6-month period following initiation of this directive.
Methods: Referrals by local GPs to our twice-weekly breast clinics were closely monitored and classified as fast-track with *proforma* (the ideal), fast-track without *proforma* and nonfast-track referrals (the former two groups were considered 'urgent', the latter nonurgent) Referral patterns and diagnostic data on cancer and all other benign conditions were collected prospectively from 1 April 1999 for 6 months
Results: A total of 1613 patients were seen over this period Some 114 cancers (7 per cent) were diagnosed, 450 (28 per cent) patients were classed as fast-track with *proforma*, 607 (38 per cent) as fast-track without *proforma* and 557 (34 per cent) as nonfast-track referrals The most frequent noncancer diagnosis was fibroadenosis in 479 (30 per cent) patients, 73 per cent of whom were referred as fast-track/urgent Of those patients with cancer, 88 of the 114 were referred as urgent; 58 (51 per cent) were referred with a *proforma* Of most interest and concern were the 26

(23 per cent) cancer patients who were referred as nonfast-track (i.e nonurgent).
Conclusions: Our figures clearly demonstrate inappropriate referral patterns from primary care A significant proportion of patients with breast cancer do not have urgent referral, unlike the majority of patients with benign conditions. Addressing this clinical observation could save considerable resources.

Breast 005

The 'two-week wait' for suspected breast cancer; its impact on a symptomatic breast unit and correlation of referrals with outcome

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Aims: The new guideline is intended to ensure that patients suspected of having breast cancer (SBC) are seen quickly by specialist teams. This study looks at the impact of such guidelines on referral numbers and assesses the accuracy of referral letters in relation to clinical findings and final diagnosis.
Methods: An audit of referral numbers and patterns between 1 August and 30 November 1997, 1998 and 1999 For 1999, referrals were categorized as SBC. requiring appointment in 2 weeks, if the GP used a specially designed fax form for SBC or gave suspicious clinical findings in an ordinary letter.
Results: Total new referral numbers in these periods in 1997, 1998 and 1999 were 608, 853 and 958 respectively. SBC referrals in August, September, October and November 1999 were 37, 40, 61 and 73 respectively. The number of breast cancers diagnosed in these referrals were 6/37 (6·2 per cent), 3/40 (7·5 per cent), 7/61 (11 4 per cent), 17/73 (23·2 per cent) Some 117 (55·5 per cent) SBC referrals were received within 24 h as in the new guidelines, but 94/211 (44·5 per cent) arrived over 24 h from the decision to refer. Between 1 August and 31 October 1999, a total of 62 new breast cancers were diagnosed, 38 (61 per cent) of these were referred as SBC, but 19 (30 per cent) were allocated lower priority on the basis of the information supplied by the GP (6/62 awaited).
Conclusions: Referral numbers have increased and the 'two-week' rule means that those referrals as SBC take urgent clinic space. A significant number of new breast cancers were not recognized as such by the GP and appointments for these patients were delayed, while some patients were seen urgently unnecessarily

Breast 006

Routine mammography for breast cysts: is it worthwhile?

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Aims: Routine mammography has been advised in women over 35-years old presenting with breast cysts. We evaluated this practice in our own patients.
Methods: A retrospective study of patients with breast cysts attending a breast clinic over a 4-year period
Results: Some 295 female patients had breast cysts. Those under 35 years of age ($n=15$) were excluded from the study Some 130 patients were under 50 years of age. Of the 186 patients who underwent mammography, two were abnormal. Both cases (aged 46 and 50 years) had independent microcalcification that proved to be malignant One of these patients had a positive family history.
Conclusions: The number of patients with breast cysts in which mammography proved useful was extremely small The routine use of mammography in women aged between 35 and 50 years is not indicated in the absence of other risk factors.

LGI 001

Transanal endoscopic microsurgery – a difficult learning curve

P. Modi, R. Gunasekera and A. Shorthouse *The Department of Surgery, Royal Hallamshire Hospital, Sheffield, UK*

Aims: To assess outcome of transanal endoscopic microsurgery (TEM).
Methods: A prospective review of all patients referred for TEM over a 6-year period in a tertiary referral centre.
Results: Of 49 patients referred, 42 underwent TEM Ten were converted intraoperatively, owing to inadequate visualization of rectosigmoid lesions (four), inability to maintain a seal at the anus (two), pump failure (one), haemorrhage (one), peritoneal breach (one) and an unsuspected ulcerated carcinoma identified during dissection (one) TEM was successfully completed in 32 patients. Of these, the preoperative diagnosis was carcinoma in eight and adenoma in 24 Postoperative histology confirmed malignancy in three adenomas. Nine patients with carcinoma diagnosed postoperatively had preoperative transrectal ultrasound; six uT1 lesions were understaged. Three patients had severe pelvic sepsis after primary suture of full thickness defects, two requiring Hartmann's procedures and one a loop colostomy. Two developed a neurogenic bladder, one of which also had a pulmonary embolus and developed retroperitoneal fibrosis and hydronephrosis. Four others had minor complications – urinary retention, haemorrhage and transient faecal incontinence (two)
Conclusions: TEM is a useful procedure but is not without significant complications in the early part of the learning curve Morbidity from pelvic sepsis may be reduced by leaving full-thickness posterior/lateral defects open to heal by granulation

LGI 002

Colorectal anastomotic leaks regularly masquerade as 'cardiac complications'

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Aims: The aim of this study was to identify the mode of presentation of patients with anastomotic leaks following restorative colorectal resection for carcinoma.
Methods: Prospective study with additional retrospective case note review. Extensive prospective information was collected on all colorectal cancer resections at our institution. These data were reviewed for a 5-year period (1994–98) to identify all the patients that had suffered an anastomotic leak Their notes were retrieved and reviewed. Patients without an anastomosis were excluded
Results: Some 379 patients underwent restorative resection for colorectal cancer during the study period (178 female, 201 male), age range 36–94 (mean 70) years. The anastomotic leak rate was 6 per cent ($n = 22$), seven (32 per cent) patients presented with obvious abdominal peritonitis. The remaining 15 (68 per cent) were initially misdiagnosed, thirteen patients (59 per cent) were treated for cardiac symptoms, one patient (5 per cent) for obstruction and one (5 per cent) for ascities The delay in diagnosis ranged from 0 to 11 days (mean 4 days). For the whole series of 379, there were 30 patients who suffered cardiac symptoms (8 per cent), 13 of which (43 per cent) had an anastomotic leak.
Conclusions: Patients who develop cardiac symptoms following restorative colorectal resection for carcinoma should have a gastrograffin enema, as there is a chance of more than 40 per cent that they have an anastomotic leak

LGI 003

Mesh repair of parastomal hernias

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Aims: Parastomal hernia is the commonest long-term complication of enterocutaneous stoma, more frequent with colostomies (5–35 per cent) than ileostomies (1–10 per cent). Around 10–20 per cent of patients develop symptoms which require surgical intervention. Results following repair are poor, with reported recurrence rates of 30–75 per cent
Methods: From 1994 to 1998, complex incisional hernias incorporating a stoma and large parastomal hernia were repaired in 10 patients using preperitoneal polypropylene mesh. Body mass index (BMI), comorbidity, length of hospital stay, patient's satisfaction and outcome were recorded
Results: There were seven females and three males, mean age 61 9 years (range, 48–80), all having primary repair The mean BMI was 31 1 (range, 20–49) Six of the 10 patients had significant comorbidity Median hospital stay was 15 days (range, 8–150) with a mean follow-up of 48 months. Three patients have had no complications. Two patients developed postoperative seroma or haematoma, requiring no intervention Wound infection occurred in two and resolved completely on antibiotics Two patients developed respiratory tract infection, one requiring ITU admission One patient developed adult respiratory distress syndrome, the stoma infarcted and, ultimately, the mesh was removed. There was no mortality and no recurrence. All but one patient was satisfied with the outcome of the operation.
Conclusions: The use of tension-free preperitoneal mesh repair for parastomal hernias in a high-risk group of patients has a low recurrence rate, offers marked improvement in outcome but may be accompanied by significant complications.

LGI 004

Anterior anal fissure and occult anal sphincter injury

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Aims: Anal fissures have classically been associated with high anal sphincteric pressures. However, postpartum and traumatic anal fissures may be linked with low anal canal pressures and are therefore derived by another mechanism We hypothesize that anterior anal fissures are commonly of this type and associated with an occult sphincter injury
Methods: This study evaluates the findings on anorectal manometry and endoanal ultrasound in a consecutive series of 15 patients presenting with anterior anal fissure
Results: Of 14 women presenting with anterior fissure, five were postpartum and a further five had previous vaginal deliveries Three fissures were associated with underlying inflammatory bowel disease or previous surgery. Endoanal ultrasound demonstrated an internal sphincter defect in nine patients and an external sphincter defect in five patients, with only three intact sphincters identified. Anorectal manometry showed a mean (±s.d.) resting pressure of 81 ± 22 mmHg and squeeze pressure of 163 ± 56 mmHg, with a trend towards lower resting pressures in internal sphincter defects (73 ± 21 mmHg)
Conclusions: These findings suggest that many patients with anterior anal fissures have an occult sphincter injury and low or normal anal resting pressures. The underlying pathophysiology is likely to be different from the classical high-pressure posterior fissures and, therefore, care should be taken when evaluating these patients to ensure that they are not made incontinent by ill-advised lateral sphincterotomy

LGI 005

A randomized trial comparing topical 0·2 per cent GTN with lateral internal sphincterotomy for chronic anal fissure with 1-year follow-up

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Aims: To compare outcomes 12 months after treatment using 0·2 per cent glyceryl trinitrate ointment (GTN) *versus* lateral internal sphincterotomy (LIS) for patients with chronic anal fissure
Methods: A prospective, randomized trial was performed and patients followed-up for 12 months
Results: Seventy patients were randomized to receive GTN (35 patients) or undergo LIS. All who underwent LIS were initially cured but one patient recurred 8 months after surgery. Nineteen of 35 patients treated with GTN experienced healing of their fissure ($P = 0{\cdot}0005$ *versus* LIS patients, χ^2 test). The remaining 16 patients randomized to receive GTN who did not experience fissure healing underwent LIS. Three patients who successfully healed with GTN suffered a recurrence within 6 months of completing treatment. The remaining 16 of 19 patients treated with GTN who experienced healing of their fissures were asymptomatic, with no clinical evidence of fissure recurrence after 12 months follow-up.
Conclusions: Lateral internal sphincterotomy remains the most efficacious method of treating patients with chronic anal fissure The majority of patients who experience healing of their fissure after LIS or topical GTN are asymptomatic 1 year after treatment

LGI 006

Diltiazem is effective treatment for chronic anal fissures

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Aims: 0·2 per cent glyceryl trinitrate ointment heals up to two-thirds of chronic anal fissures, but many patients experience troublesome headaches. This study assessed the effectiveness of oral and topical diltiazem in healing chronic fissures
Methods: Fifty consecutive patients with chronic anal fissures were randomly assigned to receive oral (60 mg) or topical (2 per cent gel) diltiazem twice daily for up to 8 weeks Anal manometry was performed before and after the first dose, and blood pressure recorded at 15-min intervals Patients were reviewed fortnightly, pain expressed using a visual analogue scale, blood pressure recorded, fissure healing assessed and side effects noted.
Results: Twenty-four patients received oral, 26 topical diltiazem. Mean (s e m.) maximum resting anal pressures fell by 15 per cent and 23 per cent from 95 (4) to 81 (4) and from 102 (5) to 79 (5) cmH$_2$O in the two groups respectively. There was no significant reduction in blood pressure during the study or at follow-up in either group. Fissure healing was complete in nine (38 per cent) patients receiving oral diltiazem and 15 (65 per cent) on topical treatment by 8 weeks. Oral diltiazem caused side effects in eight patients (rash two, headaches two, nausea or vomiting three, reduced smell and taste one), whereas topical therapy caused none.
Conclusions: Oral and topical diltiazem heal chronic anal fissures Topical diltiazem is more effective, achieving healing rates comparable with those reported with topical nitrates but without adverse effects.

LGI 007

Objective measure of specialist registrar training in a specialist coloproctology unit

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Aims: In 1998, 78 per cent of the 572 colonic resections undertaken in a single health board were performed in two dedicated coloproctology units, which has significant implications for higher surgical training in coloproctology. The objective of this audit was to analyse the training received by specialist registrars (SpRs) in a single coloproctology unit, with particular respect to the number of colonic resections.
Methods: Using prospectively collected data, index operations for coloproctology were counted for each of the 10 specialist registrars trained on the unit for the 33-month period 1 January 1997 to 30 September 1999.
Results: The median length of time on unit was 11 months (range, 6–22) In all, 540 colectomies were performed. The SpR was involved in 444 (82 per cent) cases and was surgeon in 247 (56 per cent). The consultant assisted the SpR in 185 (75 per cent) cases The SpR performed 74 per cent of the elective right hemicolectomies and 50 per cent of the elective anterior resections, with consultant assistance in 72 per cent and 85 per cent respectively. The consultant assisted the SpR in 53 per cent of the emergency right hemicolectomies and in 100 per cent of the emergency anterior resections The SpR only performed 26 per cent of the pouch operations and 11 per cent of the sphincter repair operations, with consultant assistance in 92 per cent and 100 per cent of operations respectively. In summary, SpRs staying 1 year on this coloproctology unit can expect to perform at least 24 colectomies, having consultant assistance at 75 per cent of these and be exposed to wide range level 3 specialist teaching
Conclusions: Increasing subspecialization means that only dedicated units will be able to provide adequate coloproctology training.

Paediatrics 001

Splenectomy in children: past and present

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Aims: To review the evolving role of splenectomy in children and the outcome over the past 24 years
Methods: A retrospective review of all splenectomies performed in a single regional paediatric surgical centre between 1974 and 1997. Patient demographics, indications for splenectomy, adjuvant therapy and early outcome were analysed for three consecutive 8-year time periods (1974–81, 1982–89, 1990–97)
Results: The splenectomy rate decreased from 7·5 to 2·5 per year, while the frequency of vaccination and use of prophylactic antibiotics increased There were three early deaths, owing to overwhelming sepsis, all of which occurred in the first time period (1974–81). There was no change in the complication rate between the three time periods.
Conclusions: There has been a significant reduction in the splenectomy rate over the study period associated with the use of sclerotherapy for oesophageal varices, nonoperative management of splenic injury, and advances in the medical management of haemolytic disease and ITP.

Paediatrics 002

Percutaneous endoscopic gastrostomy (PEG) feeding tubes in children: a 5-year experience in a district general hospital

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Aims: A small but significant number of children need long-term nutritional support, oral feeding is very time-consuming for parents and carers, while nasogastric tubes are unsightly and require frequent replacement The aim of this study was to evaluate the efficacy and safety of PEG feeding tubes in children.
Methods: The case notes of all children who underwent PEG insertion between 1995 and 1999 were reviewed Tubes (9F in 80 per cent) were inserted using a 'pull' technique under a short general anaesthetic.
Results: Thirty-five children were referred for PEG feeding with median age 6 years (8 months to 13 years). Twenty (57 per cent) had severe learning difficulties secondary to neurological abnormalities and 15 (43 per cent) suffered from feeding problems associated with preterm delivery, such as gastrooesophageal reflux, swallowing difficulty and food aversion. Sixteen (46 per cent) were being fed by nasogastric tube, six by gastrostomy placed during antireflux surgery and two orally. Alternative methods had been used for a median 3·5 years All 53 PEG insertions were performed successfully, of which 24 were new insertions and 30 were change of tube at the same (22) or new (eight) site PEG tubes needed changing after a mean 2 years. Thirty (56 per cent) were managed as day cases The median hospital stay for new insertions was 2 days in order to train parents/carers to use the feeding tube. Intermittent infections or discharge occurred around the insertion site in 13 cases In three patients, the gastric mucosa had grown over the 'button' of the tube, making removal difficult, and one tube translocated to the colon and was passed rectally.
Conclusions: Insertion of PEG tubes in children is a safe and simple procedure that can be performed by a general paediatric surgeon in a district general hospital. It is proposed that making this service more widely available will help children with long-term feeding problems and their carers

Paediatrics 003

Early outpatient review after paediatric day-case surgery: is it necessary?

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Aims: Outpatient review of children who had undergone day-case inguinal herniotomy, circumcision or orchidopexy is contentious The purpose of this study was to determine the extent of early postoperative problems for children who have undergone these procedures, and to assess parental attitudes to the outpatient review.
Methods: A retrospective review of 199 cases of inguinal herniotomy, circumcision and orchidopexy was performed to establish our complication rate. Parents' attitudes were canvassed using a postal questionnaire, asking of postoperative complications, if they felt that review was necessary and to give their reasons
Results: Some 199 cases were identified. Five (2·5 per cent) patients required overnight hospital stay There were 20 documented problems in 151 cases, of which 15 (75 per cent) occurred in the first week Seventeen of these patients were seen by a medical practitioner (GP 11, A&E three, OPD three) and only one had a complication that required treatment. A 58 per cent response rate for the questionnaire was recorded Sixty-four per cent of parents felt that postoperative hospital outpatient review was desirable. Thirty-two per cent felt the review was unnecessary
Conclusions: These data demonstrate that, although parents seek out professional medical reassurance for early postoperative problems that are usually minor and do not require treatment, there is no apparent health-care benefit in reviewing the child at this time As the majority of parents (64·2 per cent) preferred a formal outpatient review, principally for reassurance, methods to allay parental anxiety should be assessed in order to reduce the need for unscheduled postoperative medical contacts and early postoperative review.

Paediatrics 004

Specialist registrar training in paediatric laparoscopic surgery

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Aims: Diagnostic and interventional laparoscopic techniques have been introduced into many aspects of paediatric practice since 1990 With only some training units practising laparoscopic techniques, the aim of this study is to assess the availability of laparoscopic training to satisfy college, European or US endoscopic recommendations
Methods: All trainees (SpR) registered with the Paediatric Surgical Advisory Committee were sent a postal questionnaire to ascertain current opinions about laparoscopic surgery, and the quantity and quality of their training in laparoscopic techniques
Results: Forty-seven of the 53 trainees (89 per cent) returned a completed questionnaire. All trainees consider diagnostic laparoscopy as an important part of future practice and 78 per cent, given appropriate training, would consider interventional laparoscopic surgery Some 78 per cent would consider performing a fundoplication laparoscopically, 57 per cent a cholecystectomy, 57 per cent a stage 1 Fowler–Stevens, 47 per cent an appendicectomy, 15 per cent a urological procedure and 15 per cent a pyloromyotomy The quantity of exposure to laparoscopic techniques is disappointing On average, a paediatric trainee performs three diagnostic procedures per year (range, 0–8) and is involved in 3·4 interventional procedures (range, 0–11·6), of which the trainee performs 1·1 cases each year (range, 0–10) Only 17 per cent of trainees feel that they are receiving a satisfactory level of training in laparoscopic surgery
Conclusions: Deficient exposure to laparoscopic surgery needs to be addressed if a generation of children and surgeons are not to be disadvantaged by insufficient training, if necessary by collaboration with adult units to achieve accredited training.

Vascular 001

Infrainguinal bypass for severe limb ischaemia: 1983–98

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Aims: There has been an increasing tendency to treat severe limb ischaemia (SLI) by means of percutaneous transluminal angioplasty (PTA). The aim here is to determine the effect of this trend on the requirement for, and outcome of infrainguinal bypass surgery.
Methods: Interrogation of a prospectively gathered computerized database identified 1065 operations performed on 991 patients. During the same period, 334 PTAs were performed. Two 8-year periods have been compared
Results:

	1983–90	1991–98	*P* value
Operations (patients)	517 (483)	548 (508)	
Male female	316 (65%) 167 (35%)	285 (56%) 223 (44%)	NS[a]
Above/below knee/tibial (*n*(%))	282(55)/167(32)/68(13)	235(43)/212(39)/101(18)	<0·001[a]
Vein/vein+cuff/synthetic (*N*(%))	334(65)/12(2)/171(33)	261(47)/125(23)/162(30)	<0·01[a]
Primary patency (limb salvage) at 36 months (%)			
Above/below knee/ tibial	55(72)/64(78)/49(73)	59(77)/59(77)/47(65)	NS[b]
Vein/vein+cuff/ synthetic	61(78)/71(92)/50(66)	69(81)/44(64)/49(75)	NS[b]
PTAs (*n*)	67	277	

1983–90 compared with 1991–98 [a]χ^2, [b]log-rank test

Conclusions: A fourfold increase in the number of PTAs performed for SLI in this unit over the study period has not been associated with a reduction in bypass surgery Despite a significant increase in tibial bypass, the patency and limb salvage rates have not deteriorated, possibly because of an increase in the use of vein and vein cuffs.

Vascular 002

The search for alternative sources of autologous vein for infrainguinal bypass – is it worth the trouble?

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Aims: Arm veins (cephalic and brachial) and superficial femoral veins provide alternative sources of vein for infrainguinal bypass when ipsilateral long saphenous vein (LSV) is unavailable, but many vascular surgeons are still reluctant to use them, reverting to prosthetic grafts, which give poor long-term results In order to determine whether an aggressive policy to find alternative sources of autologous vein is warranted, we reviewed the results of this policy in a district general hospital.
Methods: Between April 1994 and November 1999, from a total of 165 infrainguinal reconstructions, 43 were performed on 38 patients (39 limbs) using reversed vein from alternative sources. The median age was 74 (range, 45–92). Seventeen were primary reconstructions for critical ischaemia and 26 were graft revisions for stenosis (12), occlusion (eight), blow-out (four) and false aneurysm (two). Thirty-five procedures involved a femoro-tibial graft, four a femoro-pedal graft and four a femoro-popliteal graft In 20 procedures, vein was used from a single source (brachial 17, cephalic two, superficial femoral one) but, in 23, multiple segments of vein were joined (LSV/brachial seven, LSV/cephalic one, brachial/cephalic five, LSV/brachial/cephalic five, femoral/brachial one, femoral/brachial/cephalic one, LSV/femoral one, LSV/femoral/brachial two). In one patient, the segment of cephalic vein was used in conjunction with PTFE. Patients were submitted to regular duplex surveillance postoperatively
Results: Mean follow-up was 14 months There was one early post-operative death within 30 days but, during follow-up, four patients died and one was lost to follow-up One-year patient survival was 90 per cent There were five early graft thromboses, of which four resulted in major amputations Four required later angioplasty for further graft stenoses and six had further surgery to maintain (four) or restore (two) graft patency. Primary, primary-assisted and secondary graft patency and limb salvage were 87 per cent, 90 per cent, 90 per cent and 92 per cent at 30 days, and 42 per cent, 64 per cent, 71 per cent and 84 per cent at 1 year respectively
Conclusions: Arm veins and superficial femoral veins give good medium-term patency and limb salvage for infrainguinal bypass when ipsilateral LSV is unavailable. However, further procedures are commonly required in the first year to maintain patency.

Vascular 003

Antithrombotic effect of dextran-40 and dextran-70 in peripheral vascular disease

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Aims: Patients with peripheral vascular disease (PVD) are hypercoaguable and demonstrate increased platelet aggregation. The aim of this study was to assess and compare the antithrombotic effect of dextran-40 and dextran-70 *in vitro*
Methods: Whole blood platelet aggregometry was performed with spontaneous platelet aggregation (SPA) and agonist-induced aggregation with ADP and collagen in 14 healthy controls and 14 PVD patients at dilutions of 10 per cent and 20 per cent. Thromboelastography (TEG) was also performed.
Results: Baseline 3-min SPA was significantly increased in PVD patients when compared with the control group (70·0 per cent *versus* 52·0 per cent, $P = 0·0049$) In PVD patients, there was a significant reduction in SPA with dextran-40 at 20 per cent dilution (46·9 per cent *versus* 70·0 per cent, $P = 0·0006$) and dextran-70 at 10 per cent dilution (53·9 per cent *versus* 70·0 per cent, $P = 0·0376$) with values not significantly different to the SPA of whole blood in the control group There was no significant difference in SPA with dextran-40 at 10 per cent or dextran-70 at 20 per cent dilutions, and agonist-induced aggregation remained unchanged in all dilutions for PVD patients. There was no significant change in SPA or agonist-induced aggregation with either dextran-40 or dextran-70 in the control group TEG produced a hypercoaguable profile for PVD patients. Dextran-40 at 20 per cent dilution significantly reduced this hypercoaguable state by the k (12·4 *versus* 6·6, $P = 0·0022$), angle (35·9 *versus* 52·9, $P = 0·0002$) and MA (43·5 *versus* 58·9, $P = 0·0003$) parameters which, when compared with the results of whole blood in healthy controls showed no significant difference. With dextran-70 at 20 per cent dilution, only the MA parameter was significantly reduced
Conclusions: Dextran-40 is able to reverse the hypercoaguable state found in PVD patients more effectively than dextran-70 However, these results suggest that the dose may be important and, therefore, of clinical relevance when using dextran

Vascular 004

Impact of supervised upper and lower limb exercise training programmes on quality of life

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Aims: Exercise is the mainstay of improving the walking distance in claudicants, but its effect on quality of life has yet to be established. This study assessed the impact of a supervised exercise programme on maximum walking distance (MWD) and quality of life

Methods: Forty-eight claudicants were recruited and randomized to upper limb training ($n=24$) or lower limb training ($n=24$), involving arm or leg crank ergometry at a work rate prescribed to induce submaximal heart rates. A parallel group undertook no supervised training ($n=15$). Training comprised two sessions per week for 6 weeks. MWD was determined at the beginning and end of the training programme, as was the quality of life (QoL) using the SF36 questionnaire

Results: MWD and the physical functioning (PF) and role limitation physical (RLP) domains of the SF36 improved in all patients who underwent training (Table)

	MWD		SF36 - PF		SF36 - RLP	
	Pre	Post	Pre	Post	Pre	Post
Upper limb group	267 (190–340)	392* (340–440)	42 (25–66)	65* (33–99)	68 (30–84)	84* (70–100)
Lower limb group	234 (200–340)	357* (275–430)	34 (0–50)	66* (33–88)	52 (0–66)	78* (44–88)
Untrained group	272 (200–340)	277 (201–342)	40 (24–66)	42 (18–56)	63 (44–90)	70 (33–99)

Data are median (interquartile range) $^*P<0{\cdot}05$ *versus* pretraining, Wilcoxon signed ranks test

Conclusions: Both upper-body and lower-body exercise training induce symptomatic and certain QoL improvements in claudicants.

Vascular 005

Do patients with critical ischaemia undergo multiple amputations after bypass surgery?

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Aims: It has been suggested that a primary major amputation may have been more appropriate in some patients undergoing surgical reconstruction for critical limb ischaemia to avoid multiple sequential amputations culminating in a major proximal amputation.

Methods: We have performed a retrospective review, over a period from April 1991 to March 1999, of patients undergoing femoral/popliteal/distal reconstruction· 590 patients underwent 711 bypass operations.

Results: Some 104 (15 per cent) of patients subsequently had one or more amputations, of which 77 were classified as major (above or below knee) The overall risk of a major amputation following arterial bypass surgery was 11 per cent. Thirteen of the initial amputations were later repeated at a higher level, giving a 2 per cent chance of multiple sequential amputations. The risk of subsequent amputations was clearly higher in the popliteal (i e crural) graft group, with the higher risk of amputation in the popliteal/distal vein groups Prosthetic grafts were used when no autogenous vein suitable for grafting was available. Emergency reconstructions had a significantly greater risk of amputations (χ^2, $P<0{\cdot}01$) Age or sex was not a significant risk factor for major amputations.

Conclusions: Patients undergoing femoral/popliteal/distal surgery for critical ischaemia are not frequently subjected to multiple, sequential amputations (2 per cent). We continue to support an aggressive policy of vascular reconstruction and preservation of a functional limb with appropriate debridement and minor amputation as necessary.

Vascular 006

Arterial perforation during angioplasty – outcomes of 1409 cases

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Aims: To assess the prevalence and clinical significance of arterial perforation during lower-limb angioplasty, and to measure the outcomes of patients suffering this complication

Methods: The radiology records of 1409 patients undergoing peripheral angioplasty between January 1996 and December 1998 were studied. Patients with a perforated vessel were identified and their clinical records examined.

Results: Fifty-two perforations occurred (3·7 per cent of all cases). Patients with a perforation were significantly older (74·8 years *versus* 69·6, $P=0{\cdot}03$) and were more likely to be diabetic ($P=0{\cdot}01$) The median age of a smoker with a perforation was 68, against 78 years for nonsmokers ($P=0{\cdot}02$) Of the perforations, 29 needed no other intervention, six had temporary occlusion with a balloon, 15 were embolized with a coil, and two needed both balloon and coil treatment. Forty-six per cent of patients ultimately had a clinically successful angioplasty. Only one case needed further urgent radiological intervention Seven patients had subsequent surgical intervention, all of whom were being angioplastied to treat critical ischaemia In no case did the perforation prejudice the eventual outcome of the patient.

Conclusions: Arterial perforation during angioplasty is more likely in the elderly and in diabetics. The perforation itself does not influence the ultimate outcome of the case; rather, it is the underlying vascular pathology.

Vascular 007

Poor medium-term results of femoropopliteal subintimal angioplasty

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Aims: Subintimal angioplasty (SIA) may be more successful than conventional (intraluminal) angioplasty for treatment of long femoropopliteal occlusions. This study assesses clinical and haemodynamic outcome of SIA.

Methods: Patients with femoropopliteal occlusions treated by SIA during the past 3 years were reviewed and assessed clinically and by colour duplex.

Results: Seventy-one procedures were performed in 70 patients; 37 males and 33 females, mean age 76 years (range, 47–92 years) Indications for treatment were intermittent claudication in 33 per cent ($n=26$) and critical limb ischaemia in 63 per cent ($n=45$) Mean occlusion length was 12·9 cm (range, 2–50) Primary technical success was achieved in 75 per cent ($n=53$) The procedural complication rate was 17 per cent ($n=12$), necessitating surgical intervention in two patients (3 per cent). There were no deaths or limb loss directly related to SIA. Clinical outcome at 6 months is shown in the table.

		Claudication ($n=26$)	Critical limb ischaemia ($n=45$)
Death		0 (0%)	9 (20%)
Symptoms	Improvement	17 (65%)	–
	Unchanged	5 (19%)	–
	Deterioration	2 (8%)	–
	Limb salvage	–	25 (55%)
Surgical bypass		1 (4%)	4 (9%)
Angioplasty		1 (4%)	1 (2%)
Amputation		0	6 (13%)

Based on an intention-to-treat basis, the cumulative primary patency of SIA at 6 months was 52 per cent.

Conclusions: In this series, the clinical success of SIA was poor, owing to a high incidence of reocclusion and restenosis, despite a high initial technical success rate

Transplantation 001

Prospective audit of 201 piggyback orthotopic liver transplants to determine the optimum operative technique

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Aims: Piggyback orthotopic liver transplantation (OLT) can be performed successfully both with or without a temporary portocaval (PC) shunt. The aim of this study was to determine whether the creation of such a shunt affected patient outcome.
Methods: Morbidity and mortality data from all piggyback OLT procedures performed since October 1994 were prospectively audited utilizing a computer database χ^2 analysis and Fisher's exact test were used to compare patient groups.
Results: Some 201 piggyback OLT were performed, 84 with and 117 without a temporary PC shunt. Of the 84 shunted, 62 were elective, 15 fulminant and seven were retransplants. Of the 117 without PC shunt, 84 were elective, 17 fulminant and 16 were retransplants.

	PC shunt	No shunt	
Postop renal failure	18 (21%)	29 (25%)	NS
Hepatic artery thrombosis	3 (3·5%)	7 (6%)	NS
Primary nonfunction	2 (2·3%)	5 (4%)	NS
Biliary leak/stenosis	4 (4·7%)	9 (7·6%)	NS
Venous outflow obstruction	1 (1%)	6 (5%)	NS
30-day mortality	6 (7%)	5 (4%)	NS

Conclusions: The incidence of all the major complications associated with piggyback OLT were reduced when a temporary PC shunt was employed A large prospective randomized trial is required to investigate further this apparent difference

Transplantation 002

Comparison of open and laparoscopic live-donor nephrectomy

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Aims: Traditional open donor nephrectomy (ODN) leaves a significant wound and this raises concerns about postoperative pain and the need for a prolonged recovery period. Some of these problems may be lessened by the use of laparoscopic live-donor nephrectomy (LDN), which has recently been introduced into surgical practice. This study compares the efficacy, morbidity and donor recovery following ODN and LDN.
Methods: An initial series of LDN ($n = 12$) were compared with a historical control group of ODN ($n = 34$). LDN was performed via a transperitoneal approach. The renal artery was double liga-clipped flush with the aorta and the renal vein was divided using an endovascular stapler The kidney was removed in an endocatch bag introduced through a 6-cm pfannensteil incision. Donors were managed with a patient-controlled analgesia system (PCAS). Postoperative pain scores, return to normal activities and complications were compared in the donors. Graft function and technical complication rates were compared in the transplant recipients.
Results: (mean ± s.e.m)

		ODN ($n = 34$)	LDN ($n = 12$)	P value
Donor	Length of stay (days)	6 ± 1·8	3·9 ± 1·1	<0·001
	PCA use (h)	64 ± 18	39 ± 13	<0·001
	Return to work (weeks)	12 ± 6	5 ± 3	<0·02
Recipient	3 month Serum creatinine (μmol L^{-1})	139 ± 35	142 ± 43	NS
	Ureteric complications	0	2 (15%)	<0·08
	Graft survival	32 (94%)	13 (100%)	NS

Conclusions: Laparoscopic donor nephrectomy is technically feasible and is likely to remove many of the disincentives to living kidney donation. The initial results of kidney transplants from LDN are good but the potential for higher rates of technical complications is of some concern and much more experience will be required before the place of this new technique can be defined

Transplantation 003

Post-transplantation malignancy: 32-year experience in 1666 allografts

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Aims: The development of a malignancy is the most feared sequel of transplantation The aim of this study was to report the incidence of this complication in our transplant population over a 32-year period
Methods: Data were collated from inhouse transplant database, pathology archives, regional Cancer Surveillance and Intelligence Unit, Cincinnati Transplant Tumor Registry, European Dialysis and Transplantation Association, inpatient records, GP questionnaire and patient interview
Results: During the period June 1967 to October 1999, 1666 transplants were performed in 1436 patients using azathioprine/prednisolone (AP, $n = 461$) or calcineurin inhibitor-based immunosuppression (CI $n = 1205$). Some 397 tumours were identified (AP $n = 154$, CI $n = 243$), consisting of 390 *de novo* tumours, four transmitted tumours (two melanomas (one donor), one renal, one colonic) and three recurrences of pretransplant neoplasia (three renal). Some 83 per cent of *de novo* tumours were of dermal origin· SCC ($n = 124$), BCC ($n = 117$), Bowen's disease ($n = 79$) and melanoma ($n = 2$). Others included lymphoma ($n = 21$), gastrointestinal ($n = 16$), breast ($n = 6$), primary ($n = 5$), bronchus ($n = 4$), thyroid/renal/cervix ($n = 3$), bladder/melanoma/leukaemia/ myeloma ($n = 2$) and epiglottis ($n = 1$). The relative risks compared with the general population were as follows: Bowen's ×174, SCC ×173, lymphoma ×101, thyroid ×84, BCC ×28 and renal ×21. The time from transplant to tumour occurrence was significantly less for the CI group (5·58 *versus* 18, $P < 0·05$) Forty-four of 73 patients with nonskin tumours but only one of 324 patients with dermal neoplasia died of carcinomatosis
Conclusions: The incidence of neoplasia in our transplant cohort was 28 per cent. Data would suggest that, with prompt management, dermal tumours which account for 81 per cent of malignancies may not be as aggressive as previously believed.

Transplantation 004

Cold ischaemia further increases intrarenal resistance when nonheartbeating kidneys are pulsatile machine perfused

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Aims: Previous work has shown that intrarenal resistance increases as the degree of warm ischaemia increases. The aim of this study was to see if prolonging the period of cold time had any effect on kidneys with short warm times (15 min) and longer warm times (45 min).
Methods: Kidneys from 40 kg pigs were subjected to *in situ* warm ischaemia of 15 min ($n = 30$) or 45 min ($n = 30$) After retrieval, the kidneys were flushed and then stored by static ice storage for 2, 12, 24, 36 or 48 h. At the end of this period, the kidneys were preserved by pulsatile machine perfusion for 6 h at a systolic pressure of 60 mmHg. Perfusate flow was measured and intrarenal resistance (IRR) was calculated as mean pressure/flow.

Results: In the first 10 min of perfusion, IRR was higher in the kidneys which sustained the longer period of warm ischaemia. This was exacerbated by prolonging the cold ischaemic time, although cold ischaemia also affected the kidneys with the shorter warm ischaemic time.

Cold ischaemic time (h)	Mean IRR over first 10 min ± s.d. (mmHg mL^{-1} min^{-1})	
	15 min warm time	45 min warm time
2	2·4 (±0·07)	3·9 (±0·17)
12	3·2 (±0·23)	4·6 (±0·29)
24	3·0 (±0·06)	3·5 (±0·26)
36	4·1 (±0·17)	4·6 (±0·33)
48	4·5 (±0·40)	6·2 (±0·94)*

*$P = 0·006$

Conclusions: Early measurement of IRR does show an increase in groups with prolonged cold ischaemic times, with an almost twofold increase in IRR from 2 to 48 h cold time in both groups. The fact that the IRR is not proportionally higher following prolonged warm ischaemic plus cold ischaemic damage suggests that these two types of ischaemic damage may not be additive in effect, as has been previously suggested.

Transplantation 005

Chronic allograft nephropathy: a prospective randomized trial of cyclosporin reduction with or without rapamycin

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Aims: Both immune and nonimmune factors such as cyclosporin (CyA) toxicity are important in the pathogenesis of chronic allograft nephropathy (CAN). Rapamycin (Rapa) has immunosuppressive properties but, in addition, inhibits the cytokine-driven proliferation of smooth muscle cells and fibroblasts that play an important role in the generation of this condition. Rapa has been proposed as a possible treatment for CAN with potential benefits over CyA reduction alone. The aim of this trial was to investigate this hypothesis.

Methods: Thirty renal transplant recipients with biopsy-confirmed CAN immunosuppressed with CyA were recruited. They were randomized to receive either a 40 per cent dose reduction in CyA (to maintain trough levels at 50–75 ng L^{-1}) or a 40 per cent dose reduction in CyA with the addition of Rapa 2 mg day^{-1}. Patients were assessed at 1, 2, 4, 6, 8, 12 and 24 weeks.

Results: Both groups were well matched in terms of patient characteristics and mean time after transplantation (Rapa 84±40 *versus* control 69±30 months, $P = 0·33$) and mean CyA trough levels after dose reduction (Rapa 68±21 *versus* control 56±19 ng mL^{-1}, $P = 0·10$). Rapa trough levels had stabilized by 4 weeks with a mean of 7·7 ng mL^{-1}.

	Control ($n = 15$)		Rapamycin ($n = 15$)	
	Pre	Post	Pre	Post
Serum Cr (µmol L^{-1})	204 (44)	193 (42)**	206 (45)	204 (59)
Cr clearance[a] (mL min^{-1})	34·9 (10·0)	36·8 (9·3)*	40·1 (9·5)	41·7 (9·8)

Values expressed as mean (s.d.). [a]Cockroft and Gault formula. *$P < 0·05$, **$P < 0·025$ paired two-tailed *t*-test

Side effects from Rapa were common with the majority of patients reporting minor symptoms and demonstrating haematological or lipid abnormalities.

Conclusions: These preliminary results suggests that Rapa at a dose of 2 mg day^{-1} has no significant benefits over cyclosporin dose reduction on the renal function of patients with CAN.

Transplantation 006

The role of laparoscopy and laparoscopic ultrasound in staging hepatocellular carcinoma in patients referred for orthotopic liver transplantation

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Aims: To determine the accuracy of laparoscopy and laparoscopic ultrasound in the diagnosis of hepatocellular carcinoma, in patients referred for orthotopic liver transplantation (OLT).

Methods: Nineteen patients undergoing assessment for liver transplantation were found to have either a mass lesion on a radiological imaging study or an elevated serum alpha feto protein. Evaluation included abdominal ultrasound (90 per cent) CT scanning (70 per cent) or angiography (21 per cent), and all patients were submitted to laparoscopy and laparoscopic ultrasound (Lap US). The accuracy of all investigations was compared with the final pathology of the explanted liver after transplant or by follow-up if OLT was not performed. The distribution of lesions (multifocal *versus* unilobar), number of lesions and involvement of portal or hepatic veins was noted.

Results: Laparoscopic evaluation changed the clinical decision in 50 per cent of cases, providing critical information not available from the other studies (metastatic disease in 2/19 cases, lesions greater than 5 cm in size in 2/19 cases, multifocal disease in 2/19). Two patients evaluated for OLT for suspicion of HCC were found not to have tumour by Lap US – they had no further therapy and are disease-free at 12 months follow-up. Two additional patients were found by Lap US to have limited disease amenable to liver resection. With regard to the distribution of lesions found (multifocal *versus* unilobar), Lap US was 100 per cent accurate when compared with the final liver specimen. Lap US was also 100 per cent accurate in predicting the number of lesions. Abdominal US had a 50 per cent accuracy rate for multifocality, CT scanning a rate of 75 per cent and angiography a rate of 50 per cent. With regard to the total number of lesions, abdominal US yielded 63 per cent accuracy, angiography a rate of 50 per cent, while CT scanning identified the correct number of lesions in only 39 per cent of cases.

Conclusions: The accurate stating of hepatocellular carcinoma is crucial to successful outcome and appropriate treatment. Laparoscopy combined with Lap US examination is the most accurate modality when compared with CT scanning, abdominal US and angiography.

Transplantation 007

Tacrolimus has less fibrogenic potential than cyclosporin A in a model of renal ischaemia reperfusion injury

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Aims: Cyclosporin-based immunosuppressive regimens are associated with significant chronic nephrotoxicity, manifest in the long term mainly as graft fibrosis. There have been claims that tacrolimus is a less fibrotic drug than cyclosporin, and this study was designed to determine if there were differences in the expression of fibrosis-associated genes between the two drugs.

Methods: Male Wistar rats underwent clamping of the right renal pedicle for 45 min together with left nephrectomy. Ischaemia reperfusion (IR) injury is a known risk factor for renal transplant fibrosis, and this model has previously been shown to be associated with up-regulation of fibrosis-associated genes. Experimental groups ($n = 6$ per group) were control (IR injury only), cyclosporin (IR injury followed by cyclosporin A 10 mg kg^{-1} day^{-1} orally) and tacrolimus (IR injury followed by tacrolimus 0·2 mg kg^{-1} day^{-1} orally). Animals were culled at 4 months and renal tissue snap frozen. Messenger RNA was extracted and quantitative reverse transcriptase polymerase chain reaction used to amplify genes of interest. Expression of all genes was as a ratio to the housekeeping gene GAPDH.

Results: These are expressed as mean (s.e.) $*P < 0{\cdot}05$ *versus* control group.

	Control	Cyclosporin	Tacrolimus
Collagen III	1·15 (0·07)	1·45 (0·22)	1·05 (0·14)
TGFβ	1·46 (0·12)	1·55 (0·21)	1·13 (0·06)*
MMP2	1·02 (0·22)	0·65 (0·13)	0·94 (0·11)
MMP9	0·55 (0·14)	0·35 (0·20)	0·58 (0·10)
TIMP1	0·64 (0·02)	0·71 (0·30)	0·41 (0·05)*
TIMP2	0·48 (0·04)	0·45 (0·05)	0·40 (0·04)

Tacrolimus treatment significantly reduced the expression of TGFβ and TIMP1, both genes associated with fibrosis. Although cyclosporin treatment reduced levels of the matrix-degrading enzymes MMP2 and MMP9, this was not statistically significant.

Conclusions: These results show that tacrolimus and cyclosporin have differing effects on the genes associated with extracellular matrix turnover. This may have implications for choice of immunosuppressive agent in patients at risk of renal transplant fibrosis.

LGI 008

Retrospective evaluation of transanal endoscopic microsurgery (TEMS) for rectal adenomas and carcinoma from a single institution

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Aims: To evaluate the efficacy of TEMS as a local treatment of rectal adenoma and carcinoma
Methods: Retrospective study from April 1993 to December 1998. Ninety-five patients identified
Results: Of the 95 patients, 75 had TEMS and 20 per anal excision (adenomas, $n=58$; carcinomas, $n=17$), (male, $n=38$, female, $n=37$). Adenoma histology showed tubulovillous (48 per cent), villous (35 per cent), tubular (7 per cent) Pathological staging of carcinomas revealed Pt0 (6 per cent), pt1 (53 per cent), pt2 (23 per cent), pt3 (17 per cent). No postoperative deaths Major rectal bleed (adenoma, 3 per cent, carcinoma, 0 per cent) and transient faecal incontinence (adenoma, 2 per cent, carcinoma, 5 per cent) were noted Combined recurrence and residual disease rate for adenoma and carcinoma was 17 per cent and 11 per cent after 34 months (2–66) and 25 months (3–60) of follow-up respectively
Conclusions: TEMS can be performed with minimal complications and acceptable local recurrence rates in adenomas and cancers There is a need for randomized trials to prove the efficacy beyond doubt for carcinoma patients

LGI 009

Multidisciplinary approach to colorectal liver metastases

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Aims: Colorectal liver metastases are common and their management is complicated There are many modalities of treatment for this condition and the selection criteria vary. We present a prospective audit of our weekly multidisciplinary meeting to discuss patient management on an individual basis so that the most effective therapeutic approach both in terms of survival benefit and palliation can be determined
Methods: The first 52 consecutive patients referred with colorectal liver metastases and treated by this multimodality approach were analysed There were 22 females and 30 males Median age was 61 years (range 47–78). Some 31 per cent had disease confined to one lobe, 69 per cent had multiple metastases involving both lobes
Results: Twenty-five per cent were suitable for liver resection and had a 55 per cent 3-year survival Eight per cent received intrahepatic arterial chemotherapy and 88 per cent systemic chemotherapy These treatments were delivered within the confines of randomized clinical trials (CR05 or CR06). Fourteen patients received *in situ* ablation of their metastases either by interstitial laser photocoagulation or radio-frequency destruction The median survival of patients receiving chemotherapy was 13 months and, where *in situ* ablation was included, the median survival was 25 months
Conclusions: We believe this approach provides patients with colorectal liver metastases the opportunity of receiving the most effective therapy It also has the benefit of enabling different specialists to develop wide expertise and understanding of all available therapeutic options

LGI 010

Endoscopic-assisted stimulated gracilis neoanal sphincter

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Aims: The stimulated gracilis neoanal sphincter (SGNS) has become accepted as a treatment for end-stage faecal incontinence The multiplicity of stages of the traditional SGNS procedure and the disfiguring long leg wound remain problems We used a single-staged operation, and an endoscopic approach to mobilize the gracilis muscle from the leg
Methods: Fifteen patients have had an endoscopically assisted procedure (one bilateral) for a variety of causes of incontinence. The pedicle is identified through a groin incision. and segmental vessels are dissected and divided The tendon is released through a 2 cm incision The one-stage procedure is covered with antibiotics
Results: There has been no infection of the implanted components None of the muscles has suffered as a result of ischaemia There was one low anal fistula that was resolved successfully. One patient continues to be incontinent, five are improved and nine are entirely successful.
Conclusions: From this experience, we conclude that the SGNS can be undertaken successfully as a one-stage procedure. The muscle can be mobilized endoscopically, thus avoiding the pain and cosmetic morbidity of the long leg wound and we suggest this approach should be adopted where possible.

LGI 011

Obstetric injury to the external anal sphincter is less common than previously thought

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Aims: External anal sphincter (EAS) injury from vaginal delivery may occur in 35 per cent, although there is disparity between this figure and the number presenting with faecal incontinence
Methods: Fifty-five nulliparous women (median age, 30 years; range, 18–47) with no history of anorectal disorder had three-dimensional anal endosonography, anal manometry and questionnaire assessment of continence (0 = total continence to 24 = total incontinence), 42 days (0–139) before delivery and 72 days (46–158) after delivery
Results: There was sonographic evidence of damage postdelivery in 25 per cent However, most of this involved just the puboanalis (PA), with the EAS torn in only 5 4 per cent. EAS trauma was associated with a significant fall in maximal squeeze pressure compared with women with no sonographic evidence of damage ($P=0{\cdot}003$) or damage to only PA ($P=0\ 016$) and with a significant increase in incontinence score ($P=0\ 02$ and $P=0{\cdot}04$ respectively)

	Change postpartum	
Ultrasound result	Squeeze pressure (cm H_2O) (mean (s e m))	Incontinence score (median (range))
Normal	21 (4)	0 (-6 to 9)
PA damage only	24 (7)	1 (0 to 8)
EAS damage	77 (26)	4 (2 to 5)

Changes in squeeze pressure and incontinence scores for women with PA damage were no different from women with normal scans ($P=0\ 76$ and $P=0{\cdot}15$ respectively).
Conclusions: Refinement in anatomical interpretation with three-dimensional endosonography has shown that external sphincter damage is less common than previously reported and, although damage to puboanalis is more common, this does not appear to be functionally significant

LGI 012

Does an ileoanal pouch offer a better quality of life than a permanent ileostomy for patients with ulcerative colitis?

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Aims: Although an ileoanal pouch is widely offered to patients with ulcerative colitis, it is still not clear whether this operation offers more advantages than a permanent ileostomy. The aim of the study is therefore to determine whether patients with a pouch have a better quality of life than a matched group of patients with a Brooke ileostomy.

Methods: Nineteen patients (12 males and seven females, median age, 41 years), who had a total colectomy and ileoanal pouch formation for ulcerative colitis, were individually matched with patients who had a panproctocolectomy and ileostomy for the same illness for gender, age, socioeconomic status and time since surgery. Quality of life was assessed using the SF36 II questionnaire, the inflammatory bowel disease questionnaire (IBDQ) and a short questionnaire on body image (BI). The scores were compared using the nonparametric Wilcoxon signed rank test for paired samples. The number of operative stages as well as complications following surgery were also recorded.

Results: The results, expressed as median standardized scores, are shown in the table.

Quest	Dimension	Pouch	Stoma	*P* value
SF36 II	Physical function	95·0	90·0	0·24
	Role–physical	93·8	100	0·59
	Role–emotional	100	100	0·57
	Social function	100	100	0·81
	Mental health	85·0	75·0	0·14
	Energy/vitality	62·5	75·0	0·49
	Pain	88·9	88·9	0·21
	General health	62·0	77·0	0·70
IBDQ	Bowel function	81·7	80·0	0·32
	Systemic symptoms	80·0	83·3	0·56
	Emotional function	84·7	80·6	0·25
	Social function	95·8	91·7	0·76
	Global score	85·4	80·7	0·56
BI	Body image	88·9	77·8	0·02

Restorative proctocolectomy was associated with a significantly better perception of body image than a permanent stoma, although quality of life in general is similar in both groups. Patients who have a pouch suffer from more long-term complications than patients with an ileostomy within the same period of time (52·6 per cent *versus* 26·3 per cent, $P = 0{\cdot}014$). The median number of stages for pouch construction was 2, compared with a median of 1 stage for an ileostomy ($P = 0{\cdot}0001$)

Conclusions: Since there is a higher long-term complication rate associated with restorative proctocolectomy and more stages are involved, patients need to be counselled thoroughly before agreeing to undergo this operation

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LGI 013

Functional outcome following short-course preoperative radiotherapy

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Aims: Short-course preoperative radiotherapy has been shown to reduce local recurrence of rectal cancer. We have assessed the patient's perception of functional outcome following the introduction of short-course preoperative radiotherapy

Methods: Using a structured questionnaire, patients were interviewed about their perceptions of bowel, bladder and sexual function pre- and postsurgery + DXT.

Results: From a series of 50 consecutive patients, 33 were available for interview (23 male, 10 female). The median time from surgery was 19 months (range, 4–30). Thirteen had permanent stomas Six of 20 felt their bowel function was normal. Fourteen complained of one or more symptoms, including frequency, urgency and incontinence. Fourteen of 33 reported bladder dysfunction Specifically, frequency, urgency, incomplete emptying and incontinence Of 23 males, 14 claimed to be sexually active prior to surgery. Of these, 10 described major dysfunction and one minor after surgery. Interestingly, four of these patients felt the erectile dysfunction was worse 6 months following surgery than at 2 months

Conclusions: Short-course DXT plus surgery is associated with major morbidity in terms of functional outcome.

Vascular 008

Common iliac artery (CIA) stents: long-term results and predictors of outcome

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Aims: Stents are increasingly and successfully used as an alternative to surgery for aortoiliac disease. Their use avoids the hazards of a general anaesthetic and the potential complications of surgery. However, little is known of the long-term fate of CIA stents or of the factors which may predict outcome.
Methods: Some 91 consecutive patients (127 limbs), median age 60 years (IQR, 55–67), 59 men (65 per cent) who had stent treatment of CIA lesions were studied. Median follow-up 36 months (IQR, 20–59). Risk factors included smoking (69 per cent), heart disease (61 per cent) and diabetes (18 per cent). Indications for treatment were claudication (81, 89 per cent), rest pain (6, 6·7 per cent), blue-toe syndrome (3·3 per cent). There were 66 stenoses (52 per cent) and 61 occlusions (48 per cent). Median lesion length was 3·1 cm (IQR, 1·1–5 cm). Outcome was assessed by a combination of clinical examination, Fontaine status, ABPI and Duplex. Regression analysis was used to assess the significance of procedural and patient variables on outcome.
Results: Immediate success rate was 98 per cent. There were 13 (14 per cent) 30-day complications: one death, six stent thromboses (7 per cent), three haematomas or bleeding requiring surgery, two emboli, and one chest infection. The median ABPI increased from 0·57 (IAR, 0·31–0·85) presenting to 0·9 (IQR, 0·61–1·1) poststenting. Primary, primary-assisted and secondary patency is 89 per cent, 93 per cent, 98 per cent and 82 per cent, 91 per cent and 96 per cent at 2 and 5 years respectively. Significant predictors of poor outcome were long lesion length (greater than 3 cm, $P = 0·03$) and greater than 50 per cent stenosis of profunda femoris ($P = 0·002$), but not an occluded superficial femoral artery.
Conclusions: Stenting of common iliac lesions has a good long-term prognosis with a relatively low complication rate, especially in short lesions. It is possible that patients with profunda disease could be offered a better result by surgical bypass or stent plus profundaplasty

Vascular 009

Three-dimensional changes after endovascular repair (ER) of AAA: SAC morphology using spiral CT angiography (SCTA)

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Aims: Endograft disruption following ER has spurred the development of three-dimensional (3D) imaging. We have investigated changes in sac shape and length, and describe, for the first time, properly validated linear and 3D changes in aneurysms after ER.
Methods: Commencing 1995, from a total 176 patients, 68 were suitable for ER and treated with two generations of endograft: 27 aorto-uni-iliac (first generation home-made UCL) PTFE and 41 modular Talent (third generation custom manufactured). Follow-up with SCTA was at day 5 and 6 monthly intervals postoperatively. With the aneurysm 'edited and segmented' at 0 HU, sac volume, maximal diameters and two lengths were measured: shortest length between the lowest renal artery and bifurcation (aneurysm length, AL) and flow channel/endograft length (FL/EL). The SCTA method was validated by prior scanning of contrast-filled glass aneurysms using pyknometry and electronic callipers for volumatic and linear measurements respectively
Results: Median preop volume was 157·5 mL (quartiles, 122·3–209·3), AL was 117·4 mm (104·5–132·1) and FL was 124·3 mm (113·1–136·6). AP and transverse sac diameters were 61·8 mm (50·3–68·6) and 62·2 mm (53·1–75·3) respectively. An initial increase ($P = 0·02$) in sac volume (PTFE + 6·03; Talent + 17·4) occurred in concert with an increase in AL for PTFE (+3·2 mm, $P = 0·04$) but not Talent patients. No change in maximal diameters took place. Significant sac shrinkage ($P = 0·02$) to 94·9 (66·04–163·2) mL occurred in Talent patients up to 1 year concomitant with decreasing maximal diameters: 35·5 (26·1–49·7) mm and 40·2 (30·8–50·3) mm for AP and transverse respectively. PTFE patients exhibited changes in length only – increase in AL +14·6 mm ($P = 0·03$) and EL +16·4 mm ($P = 0·01$) at 1·5 years. There was a 10 per cent endoleak rate at 5 days subsiding to 5 per cent at 6 months, all of which were treated, and no case of graft migration or sac rupture was observed from 6–48 months.
Conclusions: Changes in sac morphology depend on the endografting system used. significant lengthening of PTFE-treated AAA and shrinkage of Talent sac volumes and diameters was observed. These changes may produce forces that will affect long-term endograft survival.

Vascular 010

Plaque echodensity predicts the presence of retinal or hemispheric symptoms in patients with severe carotid stenosis

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Aims: It has been suggested that the type of presenting hemispheric symptoms and carotid plaque echodensity may be of prognostic value. The aim of this study was to determine the differences in the echodensity of severely stenotic carotid plaques in asymptomatic patients and in those presenting with different hemispheric symptoms
Methods: Some 170 patients (126 males, 53 females) with 201 carotid bifurcation plaques (119 symptomatic, 82 asymptomatic) causing 70–99 per cent stenosis were studied with duplex following a standard scanning protocol. Thirty-three plaques were related to amaurosis fugax (AF), 56 to TIAs and 30 to stroke. B-mode images were digitized and normalized using linear scaling and two reference points: blood and adventitia. The grey-scale median (GSM) of the plaque in the normalized image was used to quantify echodensity
Results: The mean GSM of symptomatic plaques was 12·9 and of asymptomatic plaques was 28·4 ($P < 0·001$)*. In plaques related to AF, the mean GSM was 7·5 ($P \leq 0·01$)* and in those related to TIAs and stroke it was 15 and 15·2 respectively ($P = 0·6$)*. The mean degree of stenosis for symptomatic and asymptomatic plaques was 85·3 and 83·3 respectively ($P = 0·01$)*. Logistic regression analysis revealed that plaque echodensity ($P \leq 0·001$) and not the degree of stenosis ($P = 0·45$) predicted the presence of ipsilateral hemispheric symptoms. *Wilcoxon Mann–Whitney test.
Conclusions: In patients with severe carotid stenosis, symptomatic plaques are significantly more hypoechoic (low GSM) than asymptomatic ones. Plaques associated with AF are significantly more hypoechoic than those associated with hemispheric symptoms (TIAs or stroke) which have the same echodensity. These findings confirm previous results that hypoechoic plaques are more likely to be symptomatic and that carotid plaques associated with retinal (AF) *versus* cerebral ischaemia (TIAs or stroke) have a different structure in terms of echodensity which suggests a different pathophysiological mechanism.

Vascular 011

Are the immunological effects of abdominal aortic aneurysm (AAA) surgery attenuated by the endovascular approach?

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Aims: To compare the cytokine response, leukocyte receptor expression and neutrophil elastase release in patients undergoing open and endovascular AAA repair.

Methods: Immunological parameters were compared between 31 patients undergoing open AAA repair and 15 undergoing endovascular AAA stenting under general anaesthesia Blood was taken preoperatively; 1, 2 and 12h after reperfusion and on postoperative days 1, 3, 5 and 7 Neutrophil CD11b and monocyte HLA-DR expression were determined using flow-cytometry, and plasma interleukin (IL)-1, IL-6, IL-8 and elastase were measured using commercially available ELISA.

Results: IL-6 and IL-8 were significantly elevated in both groups postreperfusion. This effect was significantly greater for open repair. Elevation of plasma elastase and monocyte HLA-DR expression occurred equally in both groups. Neutrophil CD11b expression was enhanced in both groups; however, a significantly greater elevation was seen in the endovascular group.

	IL-6		IL-8		Elastase		CDllb	HLA-DR
	Pre	Max	Pre	Max	Pre	Max	change	change
Open	8 9	195 2*	3 9	15 7*	57 3	103 7*	+41%*	–53%*
Endo	11 3	138 7*†	3 1	8 2*†	55 1	95 2*	+63%*†	–53%*

*$P<0$ 05 Wilcoxon rank test (Bonferroni adjusted), †$P<0$ 05 general linear model ANOVA
Pre(operative) and Max(imum postoperative) values for elastase, IL-6 and IL-8

Conclusions: Endovascular AAA repair is associated with reduced cytokine activation compared with open repair. However, changes in cellular immune function and neutrophil degranulation-mediated injury may occur to a similar degree.

Vascular 012

Conventional duplex criteria for completion duplex imaging may be unreliable

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Aims: The detection of residual stenoses during completion imaging has been based on conventional duplex criteria, but these criteria have not been validated for data obtained under general anaesthesia. The aim of this study was to explore the validity of applying these duplex criteria to intraoperative data

Methods: Forty patients (mean age 67 ± 8 years; 24 men and 16 women) undergoing carotid endarterectomy were studied Duplex imaging was performed preoperatively, 1 day prior to surgery and intraoperatively Stenoses of more than 70 per cent were identified by an internal carotid (ICA) peak systolic velocity (PSV) of more than 125 cm s^{-1} and an ICA.CCA PSV ratio of more than 3·4.

Results: There was excellent agreement between stenosis estimates obtained from the two preoperative scans ($r=0$ 95, $P<0·001$). Comparison of stenosis estimates obtained preoperatively and intraoperatively demonstrated a poor correlation ($r=0·52$, $P<0·005$). Using preoperative stenosis estimates as the gold standard, the sensitivity of the intraoperatively measured ICA CCA PSV ratio for identifying >70 per cent stenoses was poor (55 per cent) The ICA PSV alone, using a threshold of 125 cm s^{-1}, showed high values of sensitivity (91 per cent) and specificity (83 per cent) for distinguishing >70 per cent stenoses.

Conclusions: These results demonstrate that intraoperative duplex stenosis estimates based on conventional duplex velocity criteria are inaccurate and may result in residual stenoses being missed or overestimated. These findings have significant implications for the role of duplex imaging following carotid endarterectomy.

Vascular 013

Modular devices for EVAR: complications and recommendations

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Aims: To review the incidence and probable causes of limb-related complications following AAA repair with bifurcate devices

Methods: Some 79 patients underwent endovascular aneurysm repair (EVAR) between December 1995 and January 1999. There were 72 bifurcate and seven aorto-uni-iliac procedures attempted with a primary exclusion rate of 91 per cent and a 30-day mortality of 5 per cent

Results: Of the 72 patients undergoing bifurcate repair, 68 were discharged with a graft *in situ*. Median survival is 14 5 months: 44 cases have been followed up for 12 months and 16 for 24 months with a median reduction in aneurysm diameter of 2 mm at 12 months (3 mm at 18 months). There have been 10 limb occlusions: two occurring preoperatively, two after discharge but within 1 month and six at 1–18 months The two perioperative events were related to intraprocedural or technical problems The latter events were evenly divided between disease in the native vessels or problems caused by graft limb kinking or dislocation. Two cases of distal endoleak caused by lumbar vessel refilling have been noted and are unrelated to the type of device used A further three distal endoleaks were caused either by disconnection of the contralateral limb from main device or by upward dislocation of either limb from the iliac landing site. All endoleaks were treated successfully by endovascular means.

Conclusions: Many early graft complications could be avoided by stricter patient selection and by the use of adjunctive metal stents, later distal endoleaks can be avoided by placing both limbs well down into the common iliacs, close to the internal iliac origins. Further graft development is essential to reduce late graft distortion or failure.

LGI 014

Supraregional centre for treatment of faecal incontinence by neosphincter surgery – the NSCAG project

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Aims: In 1997, the National Specialist Commissioning Advisory Group (NSCAG) funded a Supra-Regional Unit to assess patients with faecal incontinence and to treat those suitable (determined by set criteria), with an electrically stimulated gracilis neoanal sphincter (ESGN). Our aim was to audit the first 42 months of the project to demonstrate patient pathologies, complexity of cases and level of clinical support needed.
Methods: A prospective review of the referral and treatment patterns in the centre.
Results: Some 96 patients were referred, 25 anorectal atresia, five abdomino-perineal excisions of the rectum, 38 obstetric trauma, 29 other anorectal trauma. Patients had a mean of four preoperative assessments (range 2–9), 1·6 outpatient attendances (1–4), 1·4 anorectal physiology assessments (0–7), 1·3 counselling sessions (1–3). Seventy patients were suitable for further assessment, 40 per cent of whom underwent surgery and 41·4 per cent refused further treatment. Some 78·6 per cent of these patients had previously undergone anorectal surgery. Patients undergoing surgery required a mean of 3·9 admissions (1–10), 4·3 operations (1–10), 43·6 inpatient days (8–113) and were seen eight times postoperatively (2–19).
Conclusions: These results demonstrate the need for a multidisciplinary team, extensive preoperative assessment plus intensive perioperative care. However, despite intensive counselling, a high proportion of suitable candidates will not proceed to ESGN.

LGI 015

Is there a case for local excision of rectal tumours?

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Aims: The North American Colorectal Residency Programs reported that approximately one-third of the rectal cancers were treated by endoanal excision, contrary to the practice in the UK.
Methods: Information on all patients undergoing endoanal excision between 1980 and 1999 was collated from a prospectively collected database. Patients' procedures were classified as curative or palliative on the basis of histological findings.
Results: 36/341 (10·9 per cent) patients with mid/lower rectal tumours underwent endoanal excision. There were no operative deaths and only two episodes of postoperative urinary retention. Twenty-three (62·2 per cent) patients had curative local excision. Only three patients died from metastatic disease and none from or with local recurrence after 48·3 (20–99) months. Fourteen (37·8 per cent) patients underwent palliative local excision. None died from or with local recurrence and seven died from unrelated causes after 26·4 (14–65) months. Overall, 7/23 patients develop local recurrence. Six underwent a second local excision. Three of these patients subsequently had abdominoperineal resection (APR) following incomplete excision and one had APR following first local excision. In this group, there were five deaths (three distant metastasis, two unrelated causes).
Conclusions: Only 3/37 patients died from distant disease, none from local recurrence. Local excision of rectum is a safe and effective way of treating rectal cancers in a selected group of patients.

LGI 016

A prospective single-centre study comparing CT pneumocolon against colonoscopy for detecting colorectal neoplasms

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Aims: To compare CT pneumocolon against colonoscopy for detecting colorectal cancers and significant (≥1 cm) polyps.
Methods: Some 201 consecutive patients with colorectal symptoms or requiring surveillance for colorectal neoplasms underwent CT pneumocolon immediately before colonoscopy.
Results: Seventy-two patients had colorectal neoplasms on colonoscopy; there were 13 invasive cancers and 14 significant (≥1 cm) polyps. CT pneumocolon detected all 13 invasive cancers and reported two false-positives, giving a sensitivity of 100 per cent, specificity 99 per cent, positive predictive value (PPV) 87 per cent, and negative predictive value (NPV) 100 per cent. CT pneumocolon detected seven polyps ≥1 cm, with a sensitivity of 50 per cent, specificity 96 per cent, PPV 47 per cent, and NPV 96 per cent. Thirty-one patients had incomplete colonoscopies; three had invasive cancers detected on CT pneumocolon, subsequently confirmed on repeat colonoscopy (two) or laparotomy (one). CT pneumocolon also identified distant spread in six of 16 patients with invasive colorectal cancer, and detected seven extracolonic cancers, one case of Crohns disease, and one dissecting thoracic aortic aneurysms.
Conclusions: CT pneumocolon has high sensitivity and specificity for detecting invasive colorectal cancers, but not for detecting significant colorectal polyps. Therefore, CT pneumocolon is appropriate for investigating symptoms of invasive colorectal carcinoma, such as change in bowel habit, abdominal pain and weight loss, but not for rectal bleeding alone, which could arise from a polyp.

LGI 017

Is deficient mismatch repair important in non-HNPCC colorectal cancer?

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Aims: Inherited mutations in genes responsible for mismatch repair (MMR) result in the mutator phenotype that is typical of hereditary nonpolyposis colorectal cancer (HNPCC). This study examines loss of expression of the MMR genes hMLH1 and hMSH2 in CRC not associated with HNPCC.
Methods: Some 416 individuals with CRC were identified from a single surgeon's practice, and cancer tissue was stained using an immunohistochemical technique for hMLH1 and hMSH2. A family history pedigree was obtained by personal interview from all cases, and reported cases of cancer verified with cancer registry data and pathology records.
Results: Three families identified in this study met Amsterdam criteria for HNPCC. All three probands showed normal expression of hMLH1 and hMSH2. Forty-six (11 per cent) cancers showed loss of expression (LOE) of either hMLH1 ($n = 39$) or hMSH2 ($n = 7$). MMR-deficient cancers were predominantly right-sided ($n = 44$, 95·6 per cent, $P < 0·0001$). Whereas LOE of hMLH1 increased with age (0 per cent <50 years, 5·3 per cent 51–70 years, 13·9 per cent >70 years), this was not seen for hMSH2 (4·8 per cent <50 years, 2·7 per cent 51–70 years, 0·5 per cent >70 years) ($P = 0·01$)

Conclusions: MMR deficiency is found in CRC not associated with HNPCC, particularly in right-sided lesions and with increasing age. This age effect results from LOE of hMLH1, is not seen for hMSH2, and suggests that LOE of hMSH2 in CRC may indicate a germline event predisposing to cancer development.

LGI 018

Jass staging is a predictor of outcome following 'curative' resection of Dukes' B colorectal carcinoma

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Aims: The Jass classification of colorectal carcinoma grades the primary tumour using specific histological characteristics. We wished to determine whether the Jass staging was a predictor of outcome in patients with Dukes' B tumours who had undergone 'curative' surgery.
Methods: All patients who underwent surgery for colorectal carcinoma were identified from theatre records. All specimens were examined by dedicated oncological histopathologists and were staged using the Dukes and Jass classifications. Only patients staged as Dukes' B who had undergone curative resection were included. Patients were followed up at regular intervals and a retrospective examination of their notes was undertaken to determine their postoperative course. Outcomes measured included cancer-specific mortality and the presence or absence of local or systemic recurrence.
Results: Between December 1989 and January 1998, 183 patients underwent 'curative' surgery for Dukes' B tumours. The median follow-up was 44 months (range, 4–118). Fifteen patients were classified as Jass 1, 77 as Jass 2 and 91 as Jass 3. Groups were well matched in terms of adjuvant treatment. Cancer-specific mortality, local recurrence rates and the development of systemic metastases were compared between groups B^{1-2} *versus* B^3 using the log-rank test.

	(Jass 1+2) ($n=92$)	(Jass 3) ($n=91$)	P
Five-year survival (%)	82	65	0·003
Local recurrence 3 years (%)	5	6·2	NS
Systemic recurrence 5 years (%)	22	31	0·07

Conclusions: The Jass staging system provides additional prognostic information in patients following 'curative' resection of Dukes' B colorectal carcinoma.

LGI 019

Closed haemorrhoidectomy: a randomized trial of sutured *versus* stapled methods

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Aims: Local dissection prior to wound closure may contribute to increased morbidity after closed haemorrhoidectomy. This study evaluates outcome following haemorrhoidectomy with preliminary dissection (sutured) and without (stapled).
Methods: Forty patients with prolapsed symptomatic haemorrhoids were randomized to undergo sutured (group A, $n=20$) or stapled (group B, $n=20$) haemorrhoidectomy as inpatients. All were assessed preoperatively by proctoscopy, sigmoidoscopy and anal manometry. In lithotomy, under GA, diathermy haemorrhoidectomy followed by wound suture and stapled haemorrhoidectomy (57 mm proximate reloading linear cutter, Ethicon, UK) were performed in groups A and B respectively. Excised tissue was examined histologically. Postoperative analgesia and laxatives were provided, and pain scores, complications, wound healing, readmission rates and overall patient satisfaction recorded. Patients were reviewed weekly for 4 weeks, then at 3 (anal manometry repeated) and 6 months.
Results: There was no significant difference in age, gender or preoperative symptoms between groups A and B. Preoperative anal pressures were similar in both groups, but postoperative resting and squeeze pressure were significantly reduced following the stapled technique ($P=0{\cdot}02$, $P=0{\cdot}03$, Mann–Whitney). The surgeon perceived stapled haemorrhoidectomy to be easier, taking less time to perform. Isolated muscle fibres were identified histologically in both groups, but did not cause incontinence. Stapled haemorrhoidectomy resulted in less postoperative pain, higher satisfaction ($P=0{\cdot}04$, $P=0{\cdot}01$, Mann–Whitney) and faster wound healing ($P<0{\cdot}001$, Fisher's exact test). No significant difference in complications or readmission rates was demonstrated between the two groups.
Conclusions: Stapled haemorrhoidectomy is a simple effective method of haemorrhoid excision by the closed technique. It results in less postoperative pain, faster wound healing and higher patient satisfaction compared with the sutured method.

LGI 020

Is barium enema necessary in addition to flexible sigmoidoscopy for the investigation of rectal bleeding?

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Aims: The nature and extent of colonic investigation in rectal bleeding remain controversial. This study aimed to establish whether, following a successful flexible sigmoidoscopy (FS), a barium enema (BE) yielded important additional information.
Methods: Using an endoscopy unit database, patients aged over 40 years undergoing FS for rectal bleeding, between 1997 and 1999, were identified. The yield, adequacy and extent of examination were noted. These data were compared with a radiology database, establishing the same information from those patients undergoing BE.
Results: A total of 285 patients had FS and BE for rectal bleeding alone. The yield from FS was 21 cancers and 72 polyps. BE correctly identified an additional four cancers and five polyps, missed five cancers and 52 polyps. When preparation was good and FS completed to 60 cm, no left-sided cancers were missed and all right-sided lesions were heralded by left-sided polyps.
Conclusions: BE used routinely in addition to FS increases yield in the investigation of rectal bleeding. However, when preparation was good and FS completed, its use alone and to direct selectively further investigation would have been safe in 285 patients with isolated rectal bleeding.

LGI 021

Colorectal cancer (CRC) waiting times in Plymouth

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Aims: The Plymouth colorectal cancer database was established in 1997. It provides accurate, prospective data for local, regional and national audit, and will improve the quality of colorectal cancer treatment in Plymouth. This study is to evaluate waiting times for colorectal cancer patients against college and national recommendations.

Methods: Clinical data are collected by medical staff using a colour-coded structured notes *proforma* and transferred to a database by a research nurse All the data entered for 1997 have been validated by the principal author.
Results: A total of 151 CRC patients were seen in the outpatients department· 117 were referred directly to surgeons; 34 were referred initially to physicians The average waiting time for an outpatient appointment was 4 3 weeks It was 4 7 weeks for a barium enema/colonoscopy appointment The average waiting time for surgery was 3·6 weeks. For each of these appointments, patients referred initially to physicians waited longer In 1997, Plymouth patients waited for an average of 12 6 weeks (88 2 days) for colorectal cancer treatment Patients referred to physicians waited a total of 7 weeks longer than those referred to surgeons
Conclusions: (1) Plymouth waiting times are twice as high as those reported in the Wessex and Trent/Wales audits The outpatient waiting times are certainly longer than the 2 weeks recommended by the government. The introduction of our one-stop rectal bleeding clinic next year may help reduce these waiting times (2) The study confirms what has been reported elsewhere, i.e. that CRC patients wait longer for their treatment when referred to physicians It is hoped that, with the introduction of government guidelines for referral of CRC patients, GPs will refer these patients to surgeons rather than to physicians.

LGI 022

HSC 1999/999: will it reduce delays in the treatment of colorectal cancer?

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Aims: Health Service Circular 1999/999 requires that all cases of suspected colorectal cancer are seen by a specialist within 2 weeks of the GP referral. This study examines the significance of this Directive in relation to the various components of delay in the treatment of colorectal cancer.
Methods: The GP and hospital records of 100 case of proven colorectal cancer were examined and the dates of onset of symptoms, specialist referral, diagnosis and commencement of treatment were recorded.
Results: The average waiting times included 13 weeks from the onset of symptoms before reporting to a GP, 5 weeks before the GP made a specialist referral, 3 weeks before the patient was seen, 12 weeks before the diagnosis was established and 3 weeks before treatment commenced.
Conclusions: In this study, there was an average delay of 36 weeks from the onset of symptoms to the treatment of colorectal cancer but only a very small part of this delay (3 weeks) was attributable to delayed access to a specialist clinic. The major sources of delay were delayed presentation to the GP and delays in hospital investigation

General 007

Sentinel node biopsy in patients with melanoma: an open study in a district general hospital using dynamic lymphoscintigraphy

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Aims: Biopsy of the first tumour-draining lymph node (sentinel node, SN) is a minimally invasive diagnostic and staging procedure used to select patients for regional lymphadenectomy in malignant melanoma, and this obviates the need for extensive and unnecessary lymph-node dissection. The aim of this ongoing study was to use dynamic lymphoscintigraphy followed in intraoperative gamma probe to improve the yield of successful SN biopsies in patients with intermediate thickness melanoma, who would otherwise be followed up by routine surveillance only.
Methods: From March 1997 to November 1999, 32 SN biopsies were performed in 23 stage I melanoma patients (12 males, 11 females; age, 58 ± 12). Primary melanoma was located in the trunk ($n=8$), in upper limbs ($n=9$), and in lower limbs ($n=6$) Each patient was subjected to complete surgical, nuclear medical and pathologic evaluation. Within 24 h prior to surgery, Tc^{99}-m Nanacol was injected around the primary tumour for dynamic lymphoscintigraphy. At surgical, the SNs were localized using a hand-held gamma-ray detection probe, directing the surgeon to the exact location of the SNs, which were excised and subjected to histological analysis.
Results: In 83 per cent of patients, 1–4 SNs were seen within 20 min from injection of the tracer. Four patients did not have any SNs. but this happened at the beginning of the study, when sulphur colloid was used as the tracer rather than Nanacol, which has improved the SN yield to 98 per cent. Micrometastases were positive in four SNs, all primary melanoma being of nodular histology (one patient with Breslow thickness of 0·75–1·50, and three patients with Breslow thickness of 1·51–4·00). The patients with positive SNs subsequently underwent elective lymph-node dissection, yielding two further lymph nodes positive for micrometastases. In the short follow-up period, no recurrence has developed in the lymphatic drainage areas where the SN was tumour-free
Conclusions: Dynamic lymphoscintigraphic mapping and sentinel lymphadenectomy is a multidisciplinary process (surgery, nuclear medicine and pathology) that is minimally invasive, cost-effective and accurately stages melanoma micrometastases It can be successfully learned and applied in a standardized fashion with high accuracy in a district general hospital

General 008

Problems with solutions: drowning in the brine of an inadequate knowledge base

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Aims: To determine current fluid and electrolyte-prescribing practices among surgical preregistration house officers (PRHOs) and senior house officers (SHOs) and to assess their basic knowledge of fluid and electrolyte balance.
Methods: A telephone questionnaire was administered to surgical PRHOs and SHOs working in 25 teaching and district general hospitals primarily staffed by graduates of three British medical schools. Some 100 PRHOs were surveyed within 10 days of starting their first house job (group A) and a random sample of 50 of these 6–8 weeks later (group B) Another 50 PRHOs were surveyed 6–8 weeks after starting their first house job (group C) along with 50 SHOs (group D).
Results: Responsibility for prescribing lay with the PRHO in 89 per cent of instances and only 56 per cent of respondents stated that fluid balance charts were checked daily on the morning ward round. Less than 40 per cent of respondents in groups A, B and C, and only 16 per cent in group D were given any formal or informal guidelines on fluid and electrolyte-prescribing before or after commencing work on the surgical firm. All respondents in groups B and D, 86 per cent in group A and 98 per cent in group C were either very confident or reasonably confident about prescribing fluid and electrolyte On the basis of their factual knowledge, this confidence may have been misplaced. Less than half the respondents knew the sodium content of normal saline and most did not know the daily sodium requirement. Less than 10 per cent of PRHOs and only 14 per cent of SHOs knew that body weight was the best serial measure of fluid balance. Regular postoperative weighing was not practised in any of the hospitals and most postoperative fluid prescriptions were by rote rather than clinical need. Twenty-five per cent of respondents prescribed 2 L or more of normal saline per day, which is far in excess of the needs Potassium supplements were usually within the acceptable range For most of the responses, there was no statistically significant difference between the groups.
Conclusions: The level of knowledge of fluid and electrolyte balance was inadequate and prescribing practices were suboptimal. Knowledge did not appear to improve with experience.

General 009

Development of a peritoneal model for the study of gastrointestinal tumour metastasis

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Aims: Gastrointestinal tumour cells disseminate within the abdominal cavity, adhere to the peritoneum, invade the mesothelium and its basement membrane, and proliferate to form secondary metastases To gain a better understanding of this process, we aimed to develop an *in vitro* model of the human peritoneum.
Methods: Peritoneal mesothelial and fibroblast cultures were established from human omental tissue. Fibroblasts were seeded into type I collagen gels, and cultured for 7 days to form a fibrous tissue base onto which mesothelial cells were grown to confluence. Immunohistochemistry (IHC), scanning and transmission electron microscopies (SEM and TEM) were used to compare the model with human peritoneal biopsies. Tumour invasion and metastasis formation were studied using HT-29 (colonic), SW480 (colonic), BxPc (pancreatic) and MKN45 (gastric) cell lines
Results: Light microscopy and SEM confirmed the model to consist of a mesothelial monolayer on a fibrous tissue matrix. TEM revealed a surface monolayer with typical mesothelial characteristics (microvilli, lamellar bodies, extensive rough endoplasmic reticulum) Mesothelial cells showed similar biochemical characteristics to *in vivo* tissue with basement membrane production (positive staining for fibronectin, collagen IV and laminin but absent collagen III), similar integrin expression (positive $\beta 1$, $\alpha 2$, $\alpha 3$, $\alpha 5$, αv, variable $\alpha 6$ and negative $\alpha 1$ and $\alpha 4$ subunits) and expression of intercellular adhesion molecule-1 and vascular endothelial adhesion molecule. HT-29 cells exhibited heterogeneous invasion; SW480 invaded with a degree of differentiation (crypt formation, mucin production) and induced a desmoplastic response; MKN45 and BxPc invaded rapidly with diffuse matrix infiltration
Conclusions: The peritoneal model resembles *in vivo* tissue in both its physical and biochemical properties, and provides an ideal model for studying the dynamics of peritoneal metastasis and exploring therapeutic manoeuvres for its prevention

General 010

Experience with the 'Bogota bag' in the management of severe abdominal trauma

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Aims: The management of abdominal trauma in the multiple-injured patient can be difficult Abbreviated laparotomy is recognized as a technique of damage-limitation to control intestinal spillage and bleeding by suture or packing Closure of the abdomen can be difficult after this procedure and raise intra-abdominal pressure, which is implicated in the pathogenesis of multiple-organ failure.
Methods: We have applied the Bogota bag in a consecutive series of 15 patients undergoing abbreviated laparotomy. The technique involves the suture of a large transparent plastic sheet tailored to fit the abdominal wound.
Results: Over the period October 1998 to July 1999, 15 patients (11 men, four women) of mean age 36·4 years (range, 19–65) had an abbreviated laparotomy, laparostomy and placement of a Bogota bag. Surgery was performed 73 min (range 30–184) after arriving in the hospital. In three patients, Bogota bag placement was utilized to correct surgically induced trauma Four patients died within 24 h, two others at 12 and 24 days, and one at 90 days. The Bogota bag was used when bowel oedema and intra-abdominal packing made closure difficult Definitive closure could be performed within 72 h in four patients In the rest surviving longer ($n=7$), the wound could not be closed safely and was left open The Bogota bag acted as a dressing and was changed weekly. The median intra-abdominal pressure preoperatively was 36 mmH_2O (range, 26–45) and fell to 4 mmH_2O (2–9) ($n=5$, $P<0{\cdot}01$, Mann–Whitney) 1 week after treatment These patients also had a significant reduction in intra-abdominal pressure when compared with those whose abdominal wounds underwent early closure (14 mmH_2O (8–25)). The closure of the open wound became problematic in the convalescent phase, because the lateral abdominal wall musculature retracted, maintaining the laparostomy defect.
Conclusions: The Bogota bag is a simple technique that can be used in laparostomy wounds to prevent the development of the intra-abdominal compartment syndrome. It facilitates planned reoperation for definitive treatment and acts as a good atraumatic dressing to cover the exposed intestine.

General 011

Bacterial translocation and gut immune function measured using immunohistochemistry

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Aims: It has been suggested that reduced levels of immunoglobulins at the enterocyte surface may facilitate adhesion of enteric bacteria and consequent translocation. The aim of this study was to assess quantitatively the levels of secretory antibodies in the small bowel mucosa and relate this to bacterial translocation (BT) as assessed by culture of a mesenteric lymph node (MLN).
Methods: In this study, immunohistochemistry techniques were employed to measure the concentrations of plasma cells and IgA- and IgM-positive cells in the lamina propria and semiquantitatively assess mucosal surface IgA and IgM levels in small-bowel specimens obtained from 11 patients in whom positive evidence of BT had been identified in an MLN harvested at the time of laparotomy. These were compared with similar specimens obtained from 11 patients in whom an MLN had yielded no growth
Results: BT was associated with a significantly increased median concentration of plasma cells ($P<0{\cdot}01$) and IgA-positive cells ($P<0{\cdot}05$) in the lamina propria. The concentration of IgM-positive cells was also higher in these patients, although this difference was not statistically significant In addition, surface IgA and IgM concentrations were both significantly higher in the patients in whom BT had been identified ($P=0{\cdot}006$ and 0·016 respectively).
Conclusions: The results of this study suggest that BT is associated with an increased local immune response in the small-bowel mucosa.

General 012

Activities and outcome in the surgical high-dependency setting

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Aims: The high-dependency unit (HDU) provides a level of care intermediate to that of the intensive care unit (ICU) and the general ward Early studies have shown a reduction in perioperative mortality with the introduction of HDU care However, the means of identifying patients who might benefit from an HDU facility and current guidelines for admission are lacking In order to address this deficiency, accurate descriptors of HDU activity and performance are required.
Methods: A prospective study of consecutive surgical patients admitted to a designated HDU between May and December 1998. The data were collected onto specifically designed *proformas* by a dedicated audit team and are expressed as median (and range) Comparison of continuous and discrete variables by Mann–Whitney U test and χ^2 analysis, significance set at 5 per cent level.
Results: A total of 349 patients were studied with a median age of 68 (18–92) years, of whom 316 (91 per cent) had undergone surgery. Emergencies constituted 47 per cent of all HDU admissions, the majority of patients (75 per cent) directly from theatre and 10 per cent as a stepdown from ICU. Admission in 80 per cent of cases was as an expectant measure influenced by the magnitude of surgery, in contrast to 70 (20 per cent) patients who were admitted for specific therapeutic interventions. Median HDU stay was 1·9 (0·15–12·6) days, eight (2·3 per cent) patients progressed to ICU and the readmission rate to HDU was 9 per cent Nine (2·6 per cent) patients died in HDU, 30-day mortality was 8 per cent ($n=29$) and in-hospital mortality 12 per cent ($n=42$). Thirty-day mortality was more frequent in emergency admissions (82 per cent *versus* 43 per cent, $P=0{\cdot}0001$) and significantly associated with older age (77 (45–92) *versus* 68 (18–92), $P=0{\cdot}0001$), higher POSSUM scores (39 (16–62) *versus* 34 (14–62), $P=0{\cdot}03$), a greater degree of organ dysfunction‡ (3 (0–10) *versus* (0–7), $P=0{\cdot}0001$) and higher intervention (iTISS) scores (29 (18–43) *versus* 26 (15–44)) The only pre-existing conditions associated with death were chronic airways disease and cardiac failure ($P=0{\cdot}03$), while the development of a tachyarrhythmia or renal failure more frequently resulted in death ($P=0{\cdot}01$). Until the time of death or discharge from HDU, 70 per cent of patients required physiological goal-directed interventions.
Conclusions: HDU care allows anticipation of postoperative problems and initiation of interventions early Further reductions in preventable postoperative death may be achieved by concentrating care in the high-risk groups identified in this series and by prospective evaluation of these risk factors.
Abbreviations. POSSUM, physiological and operative severity score for the enumeration of morbidity and mortality; iTISS, intermediate therapeutic intervention scoring system, ‡Marshall organ dysfunction score

HPB Pancreatic 001

Hepatic resection for noncolorectal hepatic metastases – is it worthwhile?

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Aims: Hepatic resection in selected patients with colorectal hepatic metastases (CRM) can have excellent results. However, many reports of resection of noncolorectal hepatic metastases (N-CRM) have been disappointing with high rates of tumour recurrence and early death. This study compares outcomes for patients with CRM and N-CRM undergoing hepatic resection.
Methods: Ninety-three patients with N-CRM were analysed retrospectively and their outcomes were compared with 245 patients with CRM.
Results: The N-CRM group comprised 35 patients with adenocarcinoma, 22 neuroendocrine, 16 leiomyosarcoma, three melanoma and a group of 17 patients with miscellaneous other malignancies. On the basis of staging investigations, 20 patients were found to have resectable tumours, 18 were offered chemoembolization and the remainder ($n=55$) received palliative treatment only. Although not directly comparable, surgical resection for N-CRM (median survival, 53 months) offered a significant survival benefit compared with those patients not undergoing resection (median survival, 7 months, log-rank = 11, d.f. = 1, $P<0{\cdot}001$) (Table). The survival for resected patients with N-CRM was not significantly different from that of patients with CRM (Table).

	1-year survival	2-year survival	5-year survival
N-CRM resected ($n=20$)	88%	80%	30%
N-CRM non-resected ($n=73$)	44%	32%	13%
CRM resected ($n=95$)	84%	69%	46%

Conclusions: Although numbers are small, it appears that resection for N-CRM offers as good a survival benefit as for patients with CRM. The major reason for this effect is likely to be the better prognosis of patients with neuroendocrine tumours and metastatic leiomyosarcoma.

HPB Pancreatic 002

Treatment of hepatic metastases of neuroendocrine malignancies: a 10-year experience

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Aims: Liver metastases from neuroendocrine tumours may give rise to significant symptoms, owing to hormone production or mass effect. Management options include administration of somatostatin analogues, selective chemoembolization of liver lesions or hepatic resection. We have reviewed our experience of the management of hepatic metastases of neuroendocrine tumours.
Methods: Patients with neuroendocrine tumours presenting between 1989 and 1999 were identified from pathology, radiology and surgical databases. Case notes were reviewed for demographic data, treatment modality and outcome. Response to treatment was defined as either partial or complete, based on biochemistry, radiology or symptoms.
Results: In the study period, 112 cases of gastrointestinal neuroendocrine tumours were identified. Thirty patients (one gastrinoma, 21 carcinoid, eight undifferentiated neuroendocrine tumours) initially presented with ($n=17$, 57 per cent), or later developed liver metastases ($n=13$; 43 per cent). The average age of these 30 patients at initial presentation was 55 (range, 23–81) years, the male-to-female ratio was 0·57. The site of the primary tumour was ileocoecal in 33 per cent, pancreas in 27 per cent, unknown in 20 per cent, stomach in 10 per cent and colon in 10 per cent of cases. The most frequent presenting symptoms were abdominal pain (63 per cent), diarrhoea (40 per cent), weight loss (33 per cent) and flushing (23 per cent). Five patients (17 per cent) underwent major liver resection for symptomatic carcinoid tumours (four palliative, one curative intent) without mortality and with complete response of symptoms. Nine patients (30 per cent) were treated by chemoembolization with a 75 per cent response rate (average of 1·7 embolizations per patient). Fifteen patients (50 per cent) were treated with the somatostatin analogue octreotide at some stage of their disease, with a response rate of 86 per cent. Median survivals from presentation and from detection of metastases were 60 and 40 months respectively (Kaplan–Meier analysis, SPSS9·0 for Windows).
Conclusions: Liver resection may provide good relief of symptoms, but it is only indicated in a small proportion of patients with metastatic neuroendocrine tumours. Both chemoembolization and octreotide offer useful control of symptoms in these patients whose survival prospects are good.

HPB Pancreatic 003

I-131 MIBG is cost-effective for controlling symptoms of metastatic neuroendocrine tumours

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Aims: The standard treatment used to control the symptoms of metastatic neuroendocrine tumours is octreotide. This is costly and treatment can be prolonged. The aim of this study was to evaluate the efficacy and cost-effectiveness of I-131 metaiodobenzylguanidine (MIBG) in the palliation of a large series of patients with metastatic neuroendocrine tumours.
Methods: A consecutive series of patients, referred between 1996 and 1999, with metastatic neuroendocrine tumours underwent I-131 MIBG scanning. Those patients with positive uptake underwent a course of therapeutic I-131 MIBG (200 mCi). Clinical symptoms, biochemical markers and CT scan and nuclide scan were used to assess outcome before and after treatment.
Results: There were 13 out of 23 patients who had positive uptake on I-131 MIBG scanning. Six male and seven female, with median age 62 years (range, 46–74). Eleven had metastatic carcinoid, one had metastatic gastrinoma and one had metastatic paraganglionoma. All were symptomatic. MIBG treatment was well tolerated in 11 patients. Side effects were transient. There was an 85 per cent (11/13) clinical response rate. Seven patients had complete response. Mean duration of response was 12 months (range, 3–30). There was a significant correlation between positive I-131 MIBG uptake and response rate ($P<0{\cdot}002$ Fisher's exact test). Radionuclide scan and CT scan did not show significant changes in tumour size. The use of octreotide was not required or reduced in 10 patients (77 per cent).
Conclusions: I-131 MIBG therapy is a cost-effective and safe therapeutic option for successfully controlling symptoms in patients with metastatic neuroendocrine tumours.

HPB Pancreatic 004

Radio-frequency ablation of liver tumours – experience in 151 tumours

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Aims: The latest radio-frequency (r.f.) technology using cooled-tip electrodes and high power, 200 W, makes it possible to destroy reliably

not only tumours but also a rim of normal tissue, so providing surgical margins and reducing recurrence rates. We report our experience in 151 tumours.
Methods: Some 151 tumours have been treated in 62 patients at 89 treatment sessions. The primary lesions were colorectal in 45, breast in four, hepatocellular in four, neuroendocrine in four and miscellaneous in five. Sixty-seven treatments were performed using a triple-cluster electrode with a 2·5-cm exposed tip and 22 treatments using a single electrode with a 3-cm tip Mean tumour volume treated with the triple electrode was $62\,\text{cm}^3$ (1–441) and with the single electrode $18\,\text{cm}^3$ (1–62) Some 86 treatments were percutaneous using image guidance, 51 US and MR, 33 US and CT, two US only, three were surgical, one at laparoscopy and two at open laparotomy (one in conjunction with resection of the other lobe). Thirteen were performed under conscious sedation and the remainder under GA CT was performed at 18 h to 1 week post-treatment and on follow-up at a mean of 3-month intervals (2–12).
Results: Complete tumour ablation was seen in 76 per cent. Of those who had complete ablation on initial CT, no recurrence was seen in 63 per cent at a median of 8 months There were four subcapsular haematomas, two requiring IV fluids, two pneumothoraces requiring aspiration, three abscesses, one fistula and two bile leaks treated with percutaneous drainage and IV antibiotics. The overall complication rate per treatment was 12 per cent One patient with a bile leak into the chest died.
Conclusions: Recent technological advances have resulted in adequate power to ablate completely <5 cm tumours. The next requirement is improved control.

HPB Pancreatic 005

The potential of laparoscopic ultrasonography as an alternative to operative cholangiography in the detection of bile-duct stones

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Aims: Intraoperative cholangiography (IOC) is time-consuming, involves radiation and sometimes fails, in contrast to laparoscopic ultrasonography (LUS), which is a comparatively quick, safe and noninvasive technique. The aim of this study is to assess the potential of LUS as an alternative to IOC in demonstrating ductal stones.
Methods: LUS was performed on 367 patients undergoing laparoscopic cholecystectomy. Laparoscopic duct exploration was performed in the presence of CBDS. Data were collected prospectively The presence or absence and number of duct stones (CBDS) detected by LUS were recorded. The maximum LUS bile-duct diameter was compared with a preoperative ultrasound measurement, grouped according to age and the presence of CBDS The final arbiter was the demonstration of CBDS removed at laparoscopic duct exploration (59 cases) or at subsequent ERCP (two cases of missed stones). Mean follow-up was 47 months.
Results: LUS succeeded in adequately visualizing the CBD in 98·6 per cent of cases. It correctly identified stones in 56 of the 61 patients with CBDS. No stones were demonstrated in the remaining 306 cases (sensitivity 92 per cent; specificity 100 per cent; positive predictive value 100 per cent, negative predictive value 98 per cent). LUS underestimated the total number of stones in 18 per cent of patients with CBDS The mean CBD diameter was 5·0 mm preoperatively and 5·9 mm intraoperatively in patients without CBDS, rising significantly to a mean 9·2 mm preoperatively and 11·2 mm at LUS in those with CBDS ($P<0{\cdot}0001$). The CBD diameter measured by LUS increased with age in patients without CBD stones, but not in the presence of stones.
Conclusions: LUS is a sensitive and specific method of detecting CBDS, and allows demonstration of the bile ducts and measurement of CBD diameter in almost 100 per cent of cases LUS may therefore represent a satisfactory alternative to cholangiography in the detection of bile-duct stones.

HPB Pancreatic 006

Magnetic resonance cholangiopancreatography in preoperative biliary imaging: the new gold standard?

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Aims: Magnetic resonance cholangiopancreatography (MRCP) is a safe noninvasive method of imaging the pancreatico-biliary tract, avoiding the risks associated with conventional biliary imaging modalities, including pancreatitis, ionizing radiation and iodine exposure. This study prospectively evaluates the efficacy of MRCP in imaging the common bile duct (CBD) in patients considered at risk of choledocholithiasis prior to, or after previous cholecystectomy, and further assesses the diagnosis of clinically unsuspected pathology of the liver and pancreato-biliary tract.
Methods: A consecutive series of patients with suspected biliary pathology (epigastric pain with abnormal liver function tests (LFTs), jaundice and pancreatitis) were referred for MRCP (gastroenterology referrals 25 (24 per cent); elective surgical patients 52 (41 per cent); emergency surgical admissions 29 (27 per cent)). Patients with CBD calculi diagnosed at MRCP were referred for endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy (ES) if indicated. Patients with negative MRCP findings underwent cholecystectomy with or without intraoperative cholangiography (IOC) at the discretion of the surgeon Patients with a negative MRCP undergoing laparoscopic cholecystectomy (LC) were followed up to exclude CBD calculi.
Results: A prospective series of 106 patients (74 females; median 58, range 16–92 years) underwent MRCP over a 2-year period. Indications included epigastric pain and abnormal LFTs (61 per cent), jaundice (13 per cent) and gallstone pancreatitis (12 per cent). Twenty-seven (25 per cent) patients had a previous cholecystectomy (14 OC; 12 LC; one Whipple) 28 (22–96)* months earlier. Adequate images were obtained in 102 (96 per cent) patients, with four having inadequate scans (three claustrophobia, one confused) In total, 82 (80 per cent) scans revealed no evidence of CBD calculi (true negatives). There were 14 (14 per cent) scans with unequivocal evidence of CBD calculi (true positives) confirmed in 13 cases by ERCP and ES (six), cholecystectomy and exploration of CBD (five) or percutaneous transhepatic cholangiography (two). In six (6 per cent) cases, the MRCP report suggested CBD calculi (confidently in three, possible in three). Subsequent ERCP (three), LC and IOC (two) and open exploration (one) demonstrated no calculi (false positives) Unless contraindicated, or incidental pathology was diagnosed at MRCP, the true negative group proceeded to cholecystectomy ($n=41$). In 17 (17 per cent) patients, clinically unsuspected pathology was identified on MRCP (hepatobiliary malignancy (four), choledochal cysts (two), liver cysts (five), renal pathology (two), liver haemangioma (one), primary sclerosing cholangitis (one), CBD stricture (one) and atrophic pancreas (one)). No patients with a negative MRCP have represented with choledocholithiasis during a follow-up period of 18 (10–23)* months
Conclusions: MRCP is safe and accurate in the preoperative diagnosis of CBD calculi, so reducing the requirement for more invasive risk-associated imaging techniques. Clinically unsuspected pathology may also be identified. *Median (interquartile range).

HPB Pancreatic 007

Bile leak after laparoscopic cholecystectomy

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Aims: This study of bile leakage after laparoscopic cholecystectomy estimates its incidence, identifies risk factors, demonstrates presenting symptoms and signs, evaluates tests and recommends management pathways.
Methods: It is a single-centre, retrospective study over a 9-year period (1991–99) involving all cases of laparoscopic cholecystectomy. Patients were identified using a computer word search facility for 'bile leak' and

similar expressions through the Lothian Surgical Audit database of all operation notes, endoscopy reports, discharge summaries and clinic letters. Data were extracted from computer files and case notes. The study involved cases where laparoscopic cholecystectomy was apparently completed successfully and no bile-duct injury had occurred.
Results: Twelve patients developed bile leakage after 2383 laparoscopic cholecystectomies (0·5 per cent). The median age was 57 (range, 28–70) with five males to seven females. All 12 cases were elective operations, although eight patients (67 per cent) had previous admissions for cholecystitis. Consultants operated in seven cases (58 per cent). The Calot's triangle was identified with difficulty in six patients (50 per cent) and all six had drains inserted. Five patients (42 per cent) presented during the initial hospital stay, with four having bile in the drains and one have right-upper-quadrant pain and tenderness. Seven patients were readmitted after discharge at an average of 4·4 days (range, 2–10) Common presenting features included RUQ pain and tenderness (89 per cent), anorexia and ileus (75 per cent), pyrexia (25 per cent). Eleven patients (89 per cent) had successful ERCP and stenting. One patient had a failed ERCP and proceeded to PTC with external biliary drain insertion. The site of leakage was cystic stump (nine cases), CBD (one case), duct of Luschka (one case) and unidentified (one case). Peritoneal lavage was performed in nine patients (75 per cent), seven by laparoscopy and two at laparotomy. ITU/HDU admissions were required for three patients. Average hospital stay was 19·7 days (range, 9–36). Eleven patients underwent re-ERCP at 6 weeks, all demonstrating the leak to have sealed and the stents removed There was no mortality No long-term complications have represented
Conclusions: Unsuspected bile leak after laparoscopic cholecystectomy is uncommon but carries significant in-hospital morbidity. Patients often present insidiously with vague symptoms and signs. Blood test and ultrasound scanning may be of little diagnostic value and may give false reassurance Leakage from the cystic stump was the most common source in our study. Ideal management includes early identification with ERCP, placement of a stent and relaparoscopy with extensive peritoneal lavage

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HPB Pancreatic 008

A novel 'extended' Hepp–Couinaud approach for the surgical repair of high bile-duct injuries and strictures

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Aims: The surgical repair of high biliary injuries and strictures carries a high restricture rate (up to 33 per cent). The aim of this paper is to describe the operative techniques and early results of a novel 'extended' Hepp–Couinaud approach for high injuries and strictures
Methods: Between October 1993 and April 1999, 40 patients underwent surgery for biliary injury ($n = 15$) or benign biliary stricture ($n = 25$) at our Hepatobiliary Unit. An extended Hepp–Couinaud approach was adopted in 22 patients with high injuries and strictures. There were 12 males and 28 females, with a mean age of 54 years (range, 18–79). Biliary strictures were of Bismuth's types III–IV in 54 per cent of patients. Mean follow-up was 26 months (range, 6–76).
Results: Complications developed in 12 patients (30 per cent), of whom seven were referred following a failed previous biliary reconstruction. There were two in-hospital deaths (5 per cent) at 19 and 113 days postoperatively. Recurrence of the stricture at the biliary–enteric anastomosis occurred in two patients who previously had undergone a major hepatic resection (recurrence rate, 5 per cent).
Conclusions: An extended Hepp–Couinaud approach for the repair of high biliary injuries and strictures is rewarded by a low restricture rate and is recommended

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HPB Pancreatic 009

Extensive surgery for hilar cholangiocarcinoma: early results

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Aims: Aggressive surgery for hilar cholangiocarcinoma may improve disease survival and quality of life This paper aims to describe our early results of extensive surgery for hilar cholangiocarcinoma.
Methods: Between January 1991 and July 1998, 36 patients (23 males) underwent laparotomy for radiologically operable hilar cholangiocarcinoma The disease was unresectable in seven patients, of whom two patients underwent surgical biliary bypass Resection was carried out in 29 patients (local resection two, major liver resection 19, orthotopic liver transplantation eight) and radical lymphadenectomy.
Results: The resection rate was 80·6 per cent. Hospital mortality was 9·5 per cent for resection alone and 13·8 per cent when liver transplantation was considered. Postoperative morbidity developed in 19 of 36 patients (52·8 per cent). The Kaplan–Meier 1- and 3-year actuarial survival for resection alone, transplantation and 'no resection' were 61 per cent and 37·4 per cent, 62·5 per cent and 31·3 per cent, and 21·4 per cent and 0 per cent respectively. The mean (median) cumulative survival time (including postoperative deaths) for the above three treatment modalities was 21·5 (16·7), 22·3 (18·2) and 7·9 (3·8) months respectively. Resection and transplantation significantly prolonged survival over 'no resection' ($P = 0·0257$).
Conclusions: Our early results suggest that aggressive resection for hilar cholangiocarcinoma is warranted and is associated with a favourable survival rate. Late results are awaited before transplantation could be recommended.

Breast 007

Long-term outcome of synchronous bilateral breast cancer is worse than metachronous or unilateral tumours

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Aims: There is uncertainty in the literature as to whether bilateral breast cancer carries a worse prognosis than unilateral disease. The aim of this study was to compare survival in patients with unilateral *versus* synchronous and metachronous breast cancer.
Methods: A prospectively validated database of 1947 patients was analysed for the incidence and outcome of bilateral breast cancer.
Results: A total of 92 (5 per cent) metachronous and 43 (2·2 per cent) synchronous breast cancers were identified The mean (s.d) interval between the presentation of two metachronous cancers was 9 (8) years The mean follow-up was 13 (10) years In the synchronous group, the mean overall survival was significantly shorter, 9 (9) *versus* 15 (1) years, $P<0{\cdot}05$ when compared with metachronous and unilateral breast cancer groups (log-rank test). There was no significance in survival in the unilateral and metachronous groups. Disease-free survival was also significantly shorter in the synchronous group. In both groups, nodal status was the strongest predictor of survival on Cox regression analysis ($P<0{\cdot}001$).
Conclusions: Patients with synchronous breast cancers have a worse survival than those with metachronous or unilateral breast carcinoma

Breast 008

Impact of serum CA15.3 measurement in the management of patients with carcinoma of the breast

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Aims: The role of serum CA15.3 in following up patients with breast cancer remains unclear. We asked whether an elevated CA15.3 was predictive of occult recurrence, and whether identification of such patients altered clinical management, and outcome
Methods: The setting was a district general hospital breast unit, whose policy was to stage all patients with breast cancer at diagnosis (chest X-ray, mammograms, routine blood investigations and CA15.3) and yearly thereafter The study analysed all CA15.3 measurements performed in an 8-month sample period (1 September 1998–30 April 1999) in patients with breast cancer Patients with elevated levels (above 28 U mL^{-1}) were identified and the notes reviewed The clinical status of each patient was determined, and the action taken to the elevated tumour marker noted. The outcome of those patients was followed to date, maximum follow-up 14 months Statistical analysis was performed using the Mann–Whitney *U* test.
Results: CA15.3 measurements were made in 496 patients, 78 of whom had elevated levels The groups were matched for sex (all female), but those patients with an elevated CA15.3 were significantly older than those with a normal level, although this was not an association

	CA15 3 < 28	CA15 3 > 28	Significance
Median CA15 3 (interquartile range)	16 (11–20)	39 (33–79)	$P=0\,0001$
Median age (interquartile range)	60 (52–69)	66 (58–74)	$P=0\,003$

Of the 78 patients with elevated CA15.3, 10 were patients with newly diagnosed breast cancer, and 68 were follow-ups, 37 with no evidence of recurrence, 14 with either symptoms or signs of recurrence, and 17 with known locoregional or metastatic disease. The table below shows the clinical outcome of the 37 patients with an elevated CA15.3, but no evidence of recurrence.

	Number of patients
No clinical evidence residual disease to date	29
Normal staging investigations	
Clinically detected metastases within 2 months	2
Bony metastases 1 year later, from a nonbreast primary	1
Liver metastases on CT Treated with adjuvant chemotherapy	1
Abnormal staging investigations	
Liver, pulmonary and bony metastases	3
Normal liver ultrasound and bone scan (ovarian metastases at laparotomy)	1

Of the 78 patients with an elevated CA15 3, 15 are now dead The median CA15.3 in this group [137 U mL^{-1} (73–420)] was significantly higher ($P=0\,0001$) than the 63 patients who are still alive [36 U mL^{-1} (32–45)].
Conclusions: While CA15.3 values were associated with increased mortality, the measurement of CA15.3 in patients with breast cancer was independently of value in detecting metastases and changing therapy in one patient. Thus, this study does not support the use of CA15.3 in annual staging investigations.

Breast 009

Incidence of bone metastases in early breast cancer by magnetic resonance imaging

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Aims: Magnetic resonance imaging (MRI) is a sensitive radiological method to detect asymptomatic bone metastases and differentiate between causes of vertebral compression fracture in advanced breast cancer. We aim to determine the incidence of bone metastases in asymptomatic patients at presentation with early breast cancer (EBC), and to correlate the findings to clinicopathological prognostic indices.
Methods: Fifty women with EBC presenting to a single breast unit, diagnosed by trimodality assessment (clinical assessment, mammography and cytology) as having a unilateral early breast cancer with no clinical evidence of metastases, underwent a sagittal spin echo, T1 weighted and short time inversion recovery (STIR) sequences of the thoracolumbar spine and coronal sequences through the pelvis. Films were reported by a single consultant breast radiologist.
Results: The incidence of positive MRI scans for bony metastases was 16 per cent ($n=8$, five solitary and three multiple deposits). Positive scans were significantly more common in lymph-node-positive patients than lymph-node-negative patients (33 per cent *versus* 6 per cent, $P<0\,01$, χ^2 test). No statistical difference was seen in primary tumour size, grade or ER status between the scan-positive and negative groups, although all scan-positive tumours were ER positive. Mortality at 3 years was also significantly higher in MRI positive patients compared with scan-negative patients (50 per cent *versus* 5 per cent, $P<0\,01$, χ^2 test)
Conclusions: Perioperative MRI, especially in patients who have pathological involved nodes, has the potential to identify asymptomatic bony metastases The routine use of MRI to stage early breast cancer in conjunction with histological information may enable clinicians to select patients who may benefit from early biphosphonate therapy and systemic adjuvant treatment leading to a reduction in skeletal morbidity

Breast 010

A multicentre randomized trial of a surgical and genetic clinic for high-risk women

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Aims: Women with a family history form some 10 per cent of referrals to breast clinics but there is no evidence-based management for these women

and a mixture of *ad hoc* 'family history' clinics have evolved. It is unknown whether surgeons or geneticists offer the most effective service.
Methods: This randomized trial compared the efficacy and cost of a surgical family history clinic against a specialist genetics clinic with a full gene-testing service. Endpoints were psychosocial measure, risk perception and cost over a 2-year follow-up. Both arms of the trial underwent annual mammography
Results: One-thousand high-risk women were referred and 735 were randomized to attend the clinics. The majority of women were in the moderate- or low-risk group as expected The surgical clinic gave the same reduction in anxiety as the genetics clinic measured on several scales (state-trait, anxiety, inventory and breast cancer worries scale) but neither clinic produced a lasting reduction in anxiety in the high-risk women. However, the mean surgical consultation time was 24 min (s d. = ±8·8) compared with the genetics consultation of 44 min (s.d = ±5 5). The extended genetics consultation and additional costs of testing added £61 per woman (total £25 121) for the genetics clinic.
Conclusions: This trial shows surgeons are as effective as geneticists in counselling moderate- to low-risk women at less cost but alternative strategies are required for the high-risk woman.

Breast 011

Is specimen imprint cytology the solution to the problem of positive margins during conservative breast cancer surgery?

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Aims: Further re-excision following conservative surgery is generally required for up to 30 per cent of breast cancer patients. The decision to perform a re-excision is based on the presence of close or involved specimen margins as determined from postoperative histology. We examined the potential use of specimen imprint cytology performed intraoperatively to detect the presence of positive histological margins.
Methods: Ninety-six consecutive patients with known breast cancer undergoing attempted conservative surgery were recruited. Imprints of the superior, inferior, medial and lateral surfaces of freshly excised specimens were performed using glass slides Following routine Giemsa staining, the slide cytology was later compared with standard histology of specimen margins.
Results: Of 96 specimens, 34 (35 per cent) showed histologically confirmed involved margins Twenty-two of these (65 per cent) were detected on imprint cytology. Failure routinely to sample the anterior surface was potentially responsible for four imprint failures. A further three slides were positive in the presence of negative histological margins. In two of these cases, the cavity shavings were also positive, so accurately predicting the presence of residual disease
Conclusions: The use of imprint cytology during conservative surgery could assist the localized re-excision of an involved specimen margin and eliminate the need for re-excision at a later date

Breast 012

Incidence of residual breast epithelium following mastectomy

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Aims: Women at high risk of breast cancer frequently request prophylactic mastectomy, with the assumption that mastectomy removes all breast tissue, leaving no cells from which a tumour may form. We prospectively determined the incidence and significance of residual breast epithelium in skin flaps following elective mastectomy for pre- and invasive carcinoma.
Methods: We studied the skin flaps of 106 patients undergoing mastectomy. The thickest part of the medial and lateral aspect of the upper and lower skin flaps was biopsied and examined by a pathologist for breast epithelial cells. Findings were correlated to clinicopathological prognostic indices
Results: Normal breast epithelium was found in the biopsies of 15 (14 per cent) of 106 patients. In addition, one of these patients had a residual focus of carcinoma There was no significant difference in the thickness of the skin flap between patients with positive biopsies (median, 8 mm, range, 5–10 mm) and those with negative biopsies (median, 7 mm; range, 4–20) No differences were seen between the two groups for tumour size, grade or nodal status Mortality at 3 years was not significantly increased in the biopsy positive group with two deaths from 15 patients (13 per cent) compared with seven deaths (7 5 per cent) from 91 patients

	Tumour size	Grade (%)	Nodal positive	Mortality at 3 years
Positive biopsy	Mean = 26 mm	I 27		
$n = 15$		II 53	47%	13%
	Range (11–55)	III 20		
Negative biopsy	Mean = 21 55	I 24		
$n = 91$		II 42	46%	7 5%
	Range (5–70)	III 34		

Conclusions: Complete removal of all breast tissue cannot be guaranteed by mastectomy and is not dependent on flap thickness. Patients considering prophylactic surgery must be aware of its limitations and the need for continued follow-up after surgery.

General 013

The management of soft tissue sarcoma in the Trent region

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Aims: Soft tissue sarcomas are rare and early referral to specialist centres for preoperative investigation and management by multidisciplinary teams is recommended. Trent soft tissue sarcoma group developed guidelines for the management of soft tissue sarcoma and a baseline audit has been completed to compare current practice with the guidelines
Methods: Case notes of patients with primary soft tissue sarcomas registered with Trent Cancer Registry (1 January 1995–31 December 1997) were reviewed by a single investigator (JG). Full demographic, tumour and management details were recorded for 204 cases.
Results: Fifty per cent of referrals were seen by general surgeons, 16 per cent by orthopaedic surgeons and 4 per cent by plastic surgeons. In all, 192 consultants saw a patient with soft tissue sarcoma, most seeing only one case. Median time from first hospital appointment to definitive surgery was 58 days

- *Guideline 1* – diagnostic imaging should be carried out prior to biopsy and surgery. However, 34 per cent of patients had no diagnostic imaging.
- *Guideline 2* – all patients should have staging investigations, including chest imaging: 11 per cent of patients had no X-ray or CT scan of the chest performed.
- *Guideline 3* – biopsy (needle core or incisional) should be performed before surgery. Some 37 per cent of patients did not have a biopsy before surgery and 11 per cent had an excision biopsy.

Conclusions: Soft tissue sarcoma is inconsistently managed across many specialities and sites in Trent. Current practice falls short of proposed regional management guidelines.

General 014

Informed consent – fact or fiction?

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Aims: Informed consent plays a key role in the treatment of a surgical patient and its inadequacy implies surgical intervention taking place without the patient fully understanding the consequences of surgery, which can result in profound medico-legal consequences. The aim of this study is to assess the effectiveness of consent in our surgical unit.
Methods: A questionnaire survey was conducted involving postoperative general surgical patients. Patients were reassured that their participation did not affect their treatment and the surgical teams caring for the patients were unaware of this survey
Results: The total number of patients were 100 (48 men, 52 women). The age range was 18–83 There were 62 elective and 38 emergency operations. Patients agreed that the operation was clearly explained (100); however, a significant number were uninformed of the identity of the doctor obtaining consent (52 of 48), the length of starvation (54 of 46), the length of hospital stay (50 of 50) and postoperative mobility (50 of 50)
Conclusions: Although legal consent forms were signed, a significant number of them were unaware of the identity of the doctor consenting and the operative after-care. Adequate time must be allowed for consent and we suggest an aide memoire to be included alongside the consent form

General 015

An evaluation of emergency laparoscopy in patients with an acute abdomen

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Aims: Despite the widespread use of modern imaging modalities, the acute abdomen, particularly in women of child-bearing age, remains a diagnostic challenge in emergency surgery. This study prospectively evaluates a policy of routine diagnostic laparoscopy when surgery is indicated on clinical grounds, but with no definitive diagnosis having been made
Methods: The following groups were evaluated prospectively· Group I· all females of child-bearing age in whom on clinical grounds surgery was necessary; Group II· patients with acute abdominal symptoms and signs in whom a specific preoperative diagnosis had not been made; Group III: systemically unwell patients in whom intra-abdominal pathology could not be excluded both on clinical examination and noninvasive imaging Study end-points included the definitive diagnosis or exclusion of acute intra-abdominal pathology, the need for further surgical intervention (laparotomy) and time to discharge from hospital. When indicated and where feasible, a therapeutic laparoscopic procedure was carried out (appendicectomy, cholecystectomy, peritoneal lavage). All surgical procedures were carried out (or under the direct supervision of) a single consultant surgeon experienced in diagnostic and therapeutic laparoscopy
Results: Over an 18-month period, 53 patients (35 females; median age, 26; range, 10–76 years) were eligible for the study (Group I, $n = 18$; Group II, $n = 31$; Group III, $n = 4$). The diagnoses made were as follows: Group I, appendicitis eight (44 per cent), ruptured ovarian cyst three (17 per cent), pelvic inflammatory disease three (17 per cent). Laparoscopy was negative in four (22 per cent). Group II appendicitis 16 (52 per cent), acute cholecystitis three (10 per cent), perforated duodenal ulcer (DU) one (3 per cent), diverticular abscess one (3 per cent), perforation of caecum one (3 per cent), mesenteric haematoma secondary to warfarin therapy one (3 per cent), ruptured ovarian cyst one (3 per cent) and ovarian carcinoma one (3 per cent) Laparoscopy was negative in six (19 per cent). Group III, appendicitis one (25 per cent), mesenteric infarction one (25 per cent), cholecystitis one (25 per cent). Negative findings in one (25 per cent). In total, 25 (47 per cent) appendicectomies were carried out, 11 managed (44 per cent) laparoscopically Laparoscopic cholecystectomy was carried out immediately in three cases and deferred in one case The patients with a perforated DU and diverticular abscess were successfully managed by laparoscopic peritoneal lavage alone. In patients undergoing appendicectomy, histopathology confirmed acute inflammation of the appendix in 23 (92 per cent) cases A laparoscopic procedure alone sufficed in 37 (70 per cent) cases. In two (4 per cent) cases, laparoscopy was proceeded by laparotomy (mesenteric ischaemia one, perforation of caecum one) One patient died in this series (mesenteric ischaemia). Of the patients undergoing a laparoscopic procedure, the median (range) time to discharge from the operation was 26 (18–96) h. No procedure related complications occurred.
Conclusions: Laparoscopy in the acute abdomen both improves diagnostic accuracy (with therapeutic options available) and reduces the requirement for exploratory laparotomy in systemically ill patients. The benefits of diagnostic laparoscopy are particularly evident in the women of child-bearing age presenting with abdominal pain, often resulting in a quicker postoperative recovery.

General 016

WEBS: a European Internet site for surgical teaching

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Aims: The Internet is already causing great changes in the way business is practised Applying the Internet to medical teaching could revolutionize the way we learn surgery. The aim of this project was to set up an interactive Internet site to teach European surgeons minimal access surgery; such a site has many theoretical advantages over traditional textbooks, which are expensive, not widely available and often out of date even on the day of publication.

Methods: The European Institute of Telesurgery in Strasbourg and the Minimal Access Therapy Training Unit at Guildford have collaborated to create an Internet site. A team of graphic designers and specialist Internet computer programmers have been recruited. Text, video sequences, annotated diagrams and sketches of TEP and TAPP hernia repairs, laparoscopic cholecystectomies, laparoscopic fundoplication and more advanced techniques have been assembled into an interactive web site.

Results: A standard page format has been developed which allows the reader to navigate easily their way through the site. Toolbars let the reader select video sequences, animated three-dimensional diagrams and annotated photographs which should aid learning and understanding.

Conclusions: A high-quality interactive site has been developed WEBS will be widely available through any computer with Internet access 24 h a day, continual revisions will keep the information up to date By comparison with a specialist surgical text, the cost of accessing WEBS should be minimal. The site will be demonstrated and its development and advantages over a textbook will be discussed.

General 017

Training in the Calman era: what the consultants have to say

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Aims: Over recent years, many changes have occurred in the format of surgical education, which have affected all grades of surgeons. Trainees have registered their misgivings towards training in the Calman era. However, the views of currently practising consultants on this new training system have not been sought.

Methods: A postal survey of all general surgical consultants in a single region was conducted and data collected on training, including research experience, opinions of adequacy of Calman training, importance of research, need for additional post-Calman experience, implications to patients and trainees of introducing a consultant-led service, and with regard to the need for and method of reaccredidation.

Results: The response rate was 88 per cent. Mean total postregistration training time was 11·5 years and that of specialty training was 2·5 years. Some 93 per cent had spent a defined period in research for which 88 per cent had received a higher degree Some 83 per cent felt Calman training was inadequate and 64 per cent believed future trainees would be 'junior consultants' Eighty-three per cent of respondents thought surgical trainees should be exempt from the junior doctors hours deal and 65 per cent felt the Part III exam unnecessary. Most consultants believed research should now be optional, with the majority favouring a 1-year study period However, most felt that a thesis was no longer required. Three-quarters believed a post-Calman fellowship in the area of specialist interest was advisable. Interestingly, only one-third would retrain under the new system Only one-third of consultants would participate in a resident-based consultant-led service, of which 50 per cent felt it would benefit patients and one-third felt it improved training Two-thirds agreed with the process of reaccredidation with evaluation methods split between local and external review.

Conclusions: We have demonstrated that the vast majority of consultants are concerned about the adequacy of Calman training In addition, there appears to be distinct disapproval for the introduction of consultant-led acute surgical services but reaccreditation is generally welcomed

General 018

Who operates on large bowel obstruction and who trains the SpR?

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Aims: To study operative training in emergency colonic surgery.

Methods: Data from the Association of Coloproctology and RCS of England audit of outcomes following surgery for obstruction caused by colorectal cancer has been used to determine the involvement of surgical trainees.

Results: Information from 923 cases of large-bowel obstruction caused by colorectal cancer, collected between April 1998 and March 1999, shows that consultants were the principal surgeons in 49·7 per cent of cases and were present in theatre, with an SpR operating, in 17·6 per cent. An SpR operated unsupervised in 32·7 per cent of cases For all cases admitted under a consultant who declared a special interest in colorectal surgery (CRS), the consultant operated on 56·7 per cent, assisted the SpR in 18·7 per cent and the SpR operated unsupervised in 24·6 per cent The corresponding figures for surgeons whose declared interest was other than colorectal surgery (OS) were 39·8 per cent, 16·4 per cent and 43·8 per cent. Patients admitted under a CRS are more likely to have their operation carried out by a consultant ($P<0{\cdot}001$) and less likely to have their operation carried out by an unsupervised SpR ($P<0{\cdot}001$).

Conclusions: In the post-Calman era, trainees are supervised in less than 20 per cent of operations for large-bowel obstruction and there is no difference in the level of supervision by a CRS compared with an OS. Consultant involvement, either as the principal surgeon or assistant, is significantly greater for surgeons with a declared interest in colorectal surgery

HPB Pancreatic 010

Acute cholecystitis: room for improvement?

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Aims: Recent evidence strongly favours early cholecystectomy in the management of acute cholecystitis but a recent survey of UK general surgeons showed only 10 per cent to be employing this practice Nine per cent of surgeons preferred initial conservative management, with delayed cholecystectomy (DC), and the aim of this study was to assess the outcome of this management policy.
Methods: All patients admitted with acute cholecystitis between January 1997 and June 1999 who went on to have a cholecystectomy were identified Patients were required to have right-upper-quadrant pain for >12 h, a raised white-cell count and findings consistent with acute cholecystitis on ultrasound to be included in the study
Results: Some 109 patients were admitted with acute cholecystitis (76 women, 33 men with a median age of 62 years (range, 22–88) Initial conservative management failed in 16 patients (14 7 per cent) who underwent emergency cholecystectomy as a result of continuing symptoms (nine), empyema (four) and peritonitis (three). Symptoms settled in 93 patients and DC was performed without further problems in 66 (60·6 per cent), 27 patients were readmitted with further symptoms prior to their elective surgery and, of these. three were admitted for a third time prior to surgical intervention Ten of the 30 readmission episodes (33 per cent) occurred within 3 weeks of discharge but 15 (56 per cent) occurred more than 2 months after discharge Elective surgery was undertaken at a median of 10 weeks postdischarge, with 64 per cent of operations occurring within 3 months Mean total hospital stays (days) for the three groups were as follows, emergency surgery group, 10 2; uncomplicated DC group, 12·2, readmitted group, 14·7.
Conclusions: The policy of conservative management and DC was successful in 60 6 per cent of cases, but 14 7 per cent of patients required emergency surgery and 24·8 per cent were readmitted prior to elective surgery, with a resultant increase in total hospital stay. Performing elective surgery within 2 months of discharge in all cases would have reduced the readmission rate by 56 per cent and this, along with a higher rate of early operation at the first admission, is an area where the treatment of acute cholecystitis could be improved

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HPB Pancreatic 011

Audit of the management of acute pancreatitis based on national guidelines

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Aims: To determine if the management of acute pancreatitis (AP) was in agreement with published BSG guidelines, and to identify the areas where the audit goals were not being met.
Methods: Case notes of all adult patients who had been admitted to the hospital with AP over a period of 1 year were obtained and examined in detail Demographic data, and data on aetiology of AP, prognostic investigations, imaging and various aspects of management (including use of antibiotics, ITU care and enteral and parenteral feeding) were collected Final outcome, dates and results of ERCPs, if performed, complications, if any, and data of cholecystectomy, if indicated, were also recorded.
Results: Some 95 patients (51 women) were admitted with AP over a year The age range was 19–95 years (median, 60) Fifteen patients had severe AP (based on the Atlanta classification) and four died, giving a mortality of 4·2 per cent overall, and 26 6 per cent of severe AP (within guidelines). All patients except one were diagnosed within 48 h, one at laparotomy. However, formal scoring of Glasgow criteria was recorded in the notes of only six patients. No more than 43 per cent of patients had complete prognostic investigations (excluding LDH) carried out within the first 48 h. LDH was checked in only 12 patients and CRP in six patients. Forty-two per cent did not have arterial blood gases checked or a recorded O_2 saturation of >94 per cent The aetiology of AP was gallstones in 47 per cent of patients, alcohol in 14 per cent, post-ERCP in 14 per cent and idiopathic in 19 per cent Ultrasound scans were performed within 72 h of admission in 49 per cent of patients and later in another 20 per cent Sixteen patients had staging CT scans (three without contrast), and three of these were done on the first day after admission. Six of 15 patients with severe AP had CT scans and all had grade C (<30 per cent necrosis) or D (30–50 per cent necrosis) findings. Only six patients were managed on ITU and only four had any form of tube feeding. Two patients had ERCP attempted during the acute phase of a severe attack – one failed , and ductal stones were cleared at the other Twenty-one other patients had ERCPs later on and 15 of these were normal, three failed and three had ductal stones, of which two were cleared and one stented. Some 31 patients had cholecystectomies but only one within 2 weeks and four between 2 and 4 weeks after admission with AP. The remaining 26 patients waited between 33 and 472 days (median, 87 days) for their operation. Five of these (20 per cent) were readmitted while waiting, one with severe AP.
Conclusions: While mortality figures are acceptable, prognostic investigations were complete in only 53 per cent of patients and CT scans and ERCPs are not being appropriately used in many cases. Cholecystectomies are often delayed, resulting in additional morbidity

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HPB Pancreatic 012

Assessment of BSG guidelines for the management of acute pancreatitis

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Aims: To assess the potential benefits and problems with implementation of the 'United Kingdom guidelines for the management of acute pancreatitis' (AP) issued by the British Society of Gastroenterology
Methods: Analysis of data on 211 patients with AP, managed in a single DGH over a 5-year period.
Results: Presented to correspond to each BSG recommendation (which are summarized in parentheses). *Mortality.* (<10 per cent) In hospital, 28- and 60-day mortality were 7 1 per cent, 6·3 per cent and 7·6 per cent. Of 16 deaths, 13 were >70 years and eight >80 years. *Diagnosis of AP.* Reached within 48 h in all cases (all) but one patient with equivocal amylase result had diagnostic laparotomy which could have been avoided by urgent CT. *Severity stratification.* Modified Glasgow score within 48 h in 254 of 264 admissions (all) Specificity, sensitivity. positive and negative predictive values of score were 59 per cent, 88 per cent, 0·41 per cent and 0·94 per cent respectively *CT scanning* Only 14 of 46 patients predicted severe AP had CT (all predicted severe AP within 3 and 10 days) *Aetiology of AP.* Although only 19·9 per cent idiopathic (<20–25 per cent), the diagnosis of gallstones was delayed in 13 of 121 patients with gallstone AP after suboptimal ultrasound scans. in seven, gallstones were identified on repeat ultrasound but six patients were readmitted with a recurrent AP before gallstones identified. *Treatment of mild AP.* Only 64·5 per cent of patients achieved definitive treatment of their gallstones within 4 weeks (all). Fifteen were readmitted with recurrent AP on 16 occasions before definitive gallstone treatment *ERCP* (available always). Sixty patients underwent an ERCP following AP with sphincterotomy in 49 but only three performed in the first 48 h *Predicted severe AP* Only nine of 46 managed on HDU/ITU (all), six of 165 predicted mild AP managed on ITU. All eight patients undergoing pancreatic surgery for AP managed on ITU, with mortality in two patients
Conclusions: Improvement in outcome of AP in this hospital is most likely to come from more complete and early diagnosis of gallstones, with repeat ultrasound scan in those with suboptimal scans and from early definitive treatment of gallstones once a diagnosis is reached Implementation of BSG guidelines for early CT and HDU/ITU admission for predicted severe AP would necessitate 27 CT scans and HDU/ITU

admissions in those with clinically mild AP. ITU treatment may be inappropriate for very elderly patients with severe AP.

HPB Pancreatic 013

Contemporary management of the vascular complications of pancreatitis

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Aims: To identify the incidence and evaluate the management of the vascular complications of pancreatitis, and to assess the impact of interventional radiological techniques in the management of this group of patients

Methods: Since January 1995, 294 patients have been admitted to this institution with a diagnosis of acute pancreatitis (AP) and a further 117 were treated with a final discharge diagnosis of chronic pancreatitis (CP). Patients with vascular complications were identified from departmental databases and crossreferenced with angiography suite records. Twenty-three (6 per cent) had vascular complications (21 arterial, two venous). There were 15 males and the median (range) age was 56 years (28–81) The aetiological agents were alcohol 14 (61 per cent); gallstones six (26 per cent), trauma one; steroids one; idiopathic one. Fifteen vascular complications occurred in patients with AP and eight in patients with CP.

Results: The most frequent modes of presentation of vascular complications were as follows gastrointestinal bleed in eight (35 per cent), acute abdominal pain associated with a fall in haemoglobin in seven (31 per cent) and as a bleed from an abdominal drain in five (22 per cent). The median drop in haemoglobin was 3·7 $g\,dL^{-1}$, with 19 patients requiring a blood transfusion. Median transfusion requirement was 4 (2–62) units Twelve patients (52 per cent) had evidence of hypovolaemic shock. Mesenteric angiography was performed in 20 (87 per cent) patients, revealing the following: arterial bleeding point (seven); pseudoaneurysm (seven): evidence of segmental portal hypertension (four); a pseudocyst eroding the GDA (one) and occlusion of the superior mesenteric vein (one) There were no normal angiograms. Embolization was performed in 11 cases (steel coils in five/coils plus gelatin foam six) and provided definitive haemostasis in eight. Three patients rebled within 48 h of the initial procedure. Thus, 15 (65 per cent) patients proceeded to surgery, undergoing the following procedures: pseudocyst drainage (four), splenectomy and distal pancreatectomy (three), Whipples procedure (two), necrosectomy (two), laparotomy and oversewing of bleeding point (two), splenectomy (one) and splenic artery ligation (one). The overall mortality in this group of patients was 22 per cent.

Conclusions: Stigmata of blood loss in patients with pancreatitis may herald major haemorrhage Mesenteric angiography is not only of value in localizing a bleeding point, but is also of therapeutic value as a bridging procedure. However, surgical intervention is usually indicated and is associated with a high mortality.

HPB Pancreatic 014

Efficacy of endoscopic sphincterotomy in preventing recurrent acute biliary pancreatitis

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Aims: Cholecystectomy is accepted as definitive treatment in patients with acute biliary pancreatitis, with endoscopic retrograde cholangiopancreatography plus sphincterotomy (ERCP+ES) generally being reserved for patients with significant comorbid disease The aim of this study is to assess the long-term risk of recurrent acute biliary pancreatitis and symptomatic gallbladder disease in patients with acute pancreatitis treated by ERCP+ES alone.

Methods: Some 203 patients with a discharge diagnosis of acute biliary pancreatitis identified from Lothian surgical audit records for the period November 1994 to August 1999 constituted the study population· 134 (66 per cent) underwent cholecystectomy during their index admission (or shortly thereafter), 41 (20 per cent) were treated by ERCP without cholecystectomy (18 undergoing ERCP alone and 23 ERCP+ES) and 28 (14 per cent) underwent no biliary intervention (these included patients who either declined intervention or were transferred back to referring hospitals) Data are presented as median (interquartile range)

Results: During a median follow-up of 36 (3–57) months, three (2 per cent) of the cholecystectomy group were readmitted: two with acute pancreatitis (1·5 per cent) and one (0 8 per cent) with symptomatic ductal stone disease. Of patients undergoing ERCP alone, one (13 per cent) was readmitted with acute biliary pancreatitis and, of patients undergoing ERCP+ES, two (9 per cent) had recurrent biliary acute pancreatitis. Overall, recurrent biliary acute pancreatitis after ERCP as definitive therapy occurred in 3/41 (7 per cent) No patients undergoing ERCP were subsequently admitted with gallbladder-related problems. As patients undergoing cholecystectomy were younger and with less comorbid disease, formal statistical comparison would evaluate clinically different populations and has not been performed.

Conclusions: There is an appreciable risk of late recurrent pancreatitis if ERCP+ES is used as definitive therapy for acute biliary pancreatitis While this risk may be acceptable in an older population with comorbid disease, it should be taken into consideration in addition to any immediate postprocedure risks of ERCP when deciding definitive therapy.

HPB Pancreatic 015

Risk of pancreatic cancer (PC) is greatly increased in hereditary pancreatitis (HP)

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Aims: To quantify the risk of pancreatic cancer in HP families referred to the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC)

Methods: Recruitment started in 1997, families were considered if two members had chronic pancreatitis of unknown aetiology. Families were tested for Protease Serine 1 (PRSS1) mutations using PCR restriction digestion, sequencing the PRSS1 gene screened negative families Clinical information about CP and development of PC was obtained from family members and referring clinicians. We compared the observed and expected frequency of pancreatic cancer in our historical cohort, and estimated the association of HP and PC using the standardized incidence ratio (SIR), which is the ratio of observed PC to expected PC in the background population adjusted for age, sex, nationality and surgical intervention

Results: Information was obtained on 82 families ($n = 183$) comprising 94 females and 89 males Some 31 families ($n = 79$) had the R122H mutation, 16 ($n = 44$) the N291 mutation and 35 ($n = 60$) neither mutation. Sixteen patients (eight male, eight female) mean age (95% CI) of 59 years (54·6–65·2) developed PC during 7353 person-years, compared with an expected 0 18 This yielded an overall SIR (95% CI) of 94 (70 7–107 1), an SIR of 101 3 (74 2–128·3) in males and an SIR of 91·2 (66·8–116 9) in females. The estimated overall cumulative risk (95% CI) of PC to age 75 years was 60 per cent (45per cent–75 per cent). In males, it was 70 per cent (60 per cent–95 per cent) and, in females, it was 55 per cent (40 per cent–70 per cent). The mutation statuses of the patients with PC were eight with R122H, four with N291 and four were negative

Conclusions: HP carries a significantly increased risk of PC in our cohort of patients, which equates to an estimated lifetime risk for the development of PC of 60 per cent. Men appear to have a higher risk of cancer compared with women, but the risk of PC does not appear to be related to mutation type.

HPB Pancreatic 016

Biliary drainage for obstructive jaundice enhances hepatic energy status in humans

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Aims: The pathophysiology of biliary tract obstruction is usually assessed by plasma liver function tests. We have evaluated intracellular hepatic metabolism using *in vivo* 31-phosphorus magnetic resonance spectroscopy (31P MRS), a technique that allows noninvasive assay of high-energy phosphate biochemistry.
Methods: A series of patients presenting with biochemical and radiological evidence of obstructive jaundice were studied. Hepatic energy status (measured by the ratio of adenosine triphosphate, ATP, to its hydrolysis product inorganic phosphate, Pi) and intracellular pH were determined by 31P MRS at presentation and 1 week after drainage of the biliary system.
Results: Twelve patients were investigated (nine with malignant aetiology, the remainder with benign disease). Data were analysed by repeated-measures analysis of variance and are presented as mean ± s.d.

	Bilirubin (μmol L^{-1})	Prothrombin time (s)	Energy state (ATP/Pi)	Intracellular pH
Presentation	236 ± 158	10·9 ± 1·7	1·5 ± 0·6	7·38 ± 0·10
After drainage	122 ± 114	10·7 ± 1·0	1·8 ± 0·8	7·37 ± 0·11
P value	<0·01	0·4	<0·01	0·8

Relief of obstruction resulted in enhancement of liver energy state, which paralleled the biochemical resolution of jaundice but was not evident from clotting profiles. Hepatic intracellular acid–base balance was well compensated throughout the clinical course.
Conclusions: Decompression of an obstructed biliary system is associated with recovery of high-energy phosphate metabolism, which translates into amplification of hepatocyte energy charge and, hence, functional capacity. Measurement of liver intracellular bioenergetics may have important implications for the planning of therapeutic options in jaundiced patients, particularly when hepatic resection is a consideration.

HPB Pancreatic 017

Postchemoembolization syndrome: tumour necrosis or liver parenchymal injury?

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Aims: Controversy exists as to whether the increase in temperature and transaminases commonly seen following transarterial chemoembolization (TACE) of liver tumours represents necrosis of the tumour or collateral damage to normal liver. The greatest experience of TACE is in patients with hepatocellular carcinoma (HCC) and, in this model, the significance of elevated transaminases is unclear, since the tumours may themselves retain the hepatocyte phenotype and produce these enzymes. This study compares responses to TACE in patients with primary and secondary liver cancer.
Methods: Analysis was undertaken of responses to 267 procedures undertaken using adriamycin 40 mg and lipiodol 10 mL by selective hepatic artery cannulation (89 per cent) in 145 patients with liver cancer. Patients were subdivided into those with HCC, with potential to produce transaminases (TA) ($n = 75$), and nontransaminase (NTA)-producing secondary tumours ($n = 70$).
Results: Maximal changes in liver function tests, INR and temperature are shown in the table.

	HCC (TA)		Secondary (NTA)		*P*
Albumin (g L^{-1})	–5	(–15–5)	–5	(–13–2)	0·56
AST (U L^{-1})	151	(33–1432)	188	(–8–1717)	0·02
AlkPhos (U L^{-1})	7·5	(–335–1776)	23	(–123–800)	0·012
Temperature (°C)	1·8	(0–3·2)	1·6	(0–3·4)	0·9

TACE of TA-producing tumours did not produce a more florid postchemoembolization syndrome than TACE for NTA secondary tumours. In addition, survival analysis based on the first response to TACE demonstrated that a temperature >38·5°C was a factor associated with poor prognosis (survival temp. >38·5 = 7 months, temp <38·5 = 12 months, log-rank = 10, $P = 0·0016$).
Conclusions: Responses to TACE were similar between patients with primary and secondary liver cancer. Specifically, elevation of transaminases was greater in secondary tumours than in transaminase-producing primary tumours. This suggests that the postchemoembolization syndrome represents in part damage to normal hepatic parenchyma. Furthermore, it appears that a florid response to TACE does not equate with beneficial tumour response as measured by survival.

Vascular 014

Relationship between abdominal aortic aneurysm compliance and serum markers of elastin and collagen metabolism

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Aims: Previous work suggests that abdominal aortic aneurysm (AAA) compliance is an independent predictor of future growth and rupture, possibly because it reflects changes in aortic wall structure. To determine, for the first time, whether AAA compliance is related to serum markers of elastin and collagen metabolism.
Methods: Elastic modulus (Ep) and stiffness (β) were measured using an ultrasonic echo-tracker (Diamove). Serum elastin peptide (SEP), plasma elastin-α1-antitrypsin complex (E-AT), procollagen III-N-terminal propeptide (PIIINP), matrix metalloproteinase (MMP)-2 and MMP-9 levels were measured by enzyme-linked immunoassay.
Results: There were 70 male patients of mean (range) 71 (67–76) years with asymptomatic AAA of median (IQR) diameter 42 (37–42) mm. Ep and β were significantly inversely related to SEP, indicating increased elastolysis ($r=-0·26$, $P<0·05$) Increased levels of elastose, indicated by levels of E-AT were significantly inversely related to Ep and β ($r=-0·33$, $P<0·05$). By contrast, there was a significant positive correlation between PIIINP, which indicates increased collagen turnover, and both Ep and β ($r=0\ 36$, $P<0\ 05$). MMP-2 was not significantly related to Ep or β, while MMP-9 was significantly inversely related to Ep and β in AAA $\geqslant$40 mm ($r=-0\ 61$, $r=n$ $-0·54$, $P\leqslant0·03$).
Conclusions: Increased elastolysis is associated with increased AAA wall compliance, whereas increased collagen turnover is associated with reduced compliance. Compliance may offer a noninvasive 'surrogate' marker of changes in AAA wall composition

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Vascular 015

Laparoscopic-assisted abdominal aortic aneurysm repair

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Aims: Although elective mortality from open repair of abdominal aortic aneurysm (AAA) remains at 5 per cent, morbidity is very much higher. This relates to major fluid shifts, hypothermia and acid–base abnormalities during surgery and further postoperative complications caused by the long abdominal incision. The aim of this study is to reduce complications of open repair of AAA by minimally invasive laparoscopic techniques
Methods: Ten patients (mean age, 72 years) have undergone laparoscopic-assisted repair (Lap AAA) Following abdominal insufflation with CO_2 and port placement, the neck of the AAA was dissected using laparoscopic (lap) instruments. The camera system was then directed caudally and the common iliac arteries (CIAs) dissected Standard arterial clamps were placed via small skin incisions to clamp the aorta and CIAs. The lap equipment was removed and a small supra-umbilical incision made through the abdominal wall and into the aneurysm sac, but abdominal wall and aneurysm walls are retracted with a self-retaining retractor. A standard Dacron graft was sutured into position using the inlay technique.
Results: Wound length 6·5 ± 1 cm No postcomplications. All patients remained normothermic, with no acid–base deficit, intraoperative fluid requirements 1300 ± 275 mL. Only one patient required a longer ITU stay of 1 day. All patients discharged at 7 days
Conclusions: Lap AAA appears to offer a significant reduction in morbidity. We are now conducting a randomized controlled trial.

Vascular 016

Cessation of vibration exposure in patients with the hand–arm vibration syndrome does not prevent disease progression

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Aims: The progression of disease following cessation of exposure to vibration in patients with the hand–arm vibration syndrome (HAVS) is still not fully understood. The aim of our study was to determine the effect of abstaining from vibration exposure in a group of patients with moderate-to-severe disease
Methods: Twenty-four patients (23 men, one woman; median age, 39 years; range, 29–59) with HAVS underwent two assessments with a median time of 30 5 months (IAR, 21·25–45) between them. All known causes of secondary Raynauds phenomenon were excluded. At each assessment, a detailed history of the patients' symptoms was obtained and the disease state graded using both the Taylor–Pelmear (TP) and Stockholm workshop classification scales. A detailed occupational history was obtained and the group of patients split into those who had abstained from vibration and those who had continued to use vibrating tools during the period between the two assessments
Results: Eighteen patients had abstained from vibration exposure following the initial assessment No significant difference was found in the latent period, initial length of vibration exposure or amount of time exposed to vibration per week between the two groups prior to the initial assessment ($P<0·05$, Mann–Whitney U). No significant difference in disease classification was determined between the nonvibration and vibration groups at the time of initial assessment (TP median 3 (IQR, 3–3) *versus* median 3 (IQR, 2–3) respectively). The table shows symptom progression in the two groups between the two assessments.

Symptom	Deterioration	No deterioration	P value (χ^2 test)
Pallor	**13**/4	**5**/2	0 8
Tingling	**12**/4	**6**/2	0 62
Pain	**15**/5	**3**/1	0 53
Numbness	**14**/4	**4**/2	1 00

Bold = number of subjects not exposed to vibration Nonbold = number of subjects exposed to vibration

Conclusions: Abstinence from vibration exposure does not prevent progression of disease in patients with moderate-to-severe HAVS. Measures must therefore be taken to ensure that people are initially not exposed to the levels of vibration that can cause HAVS and more stringent assessments must be made of people presenting with mild symptoms to prevent further deterioration of disease.

Vascular 017

Carotid endarterectomy or endovascular treatment for symptomatic carotid artery disease?

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Aims: To compare the stroke and death risk within 30 days of endovascular treatment or endarterectomy for symptomatic carotid artery disease.
Methods: Systematic comparison of 30-day outcome of angioplasty ± stenting and endarterectomy for symptomatic carotid artery disease reported in single-centre studies published since 1990 Main outcome measures were taken as stroke and death within 30 days of the procedure.
Results: Thirty-three studies (13 angioplasty and 20 carotid endarterectomy) were included in this analysis. Carotid stents were deployed in 44

per cent of angioplasty patients. Mortality within 30 days of angioplasty was 0·8 per cent compared with 1·2 per cent following endarterectomy (odds ratio (OR) 0·68; 95% confidence interval (CI) 0·43–1·05; $P=0{\cdot}6$). The 30-day stroke rate was 7·1 per cent for angioplasty and 3·3 per cent for endarterectomy (OR 2·22; CI 1·62–3·04; $P<0{\cdot}001$), while the risk of fatal or disabling stroke was 3·2 per cent and 1·6 per cent respectively (OR 2·09, CI 1·3–3·33; $P<0{\cdot}01$). The risk of stroke or death within 30 days was 7·8 per cent for angioplasty and 4 per cent for endarterectomy (OR 2·02, CI 1·49–2·75; $P<0{\cdot}001$), while disabling stroke or death was 3·9 per cent after angioplasty and 2·2 per cent following endarterectomy (OR 1·86, CI 1·22–2·84; $P<0{\cdot}01$).
Conclusions: In the treatment of symptomatic carotid artery disease, the risk of stroke is significantly greater within 30 days of angioplasty than for carotid endarterectomy. At present, endovascular treatment is not recommended for the majority of patients with symptomatic carotid artery disease

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Vascular 018

In situ prosthetic reconstruction for suprarenal mycotic aneurysms of the aorta

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Aims: Mycotic aneurysms of the suprarenal aorta present a surgical challenge A review of the management and results of both ruptured and nonruptured mycotic aneurysms of the suprarenal aorta in a single institution over a 6-year period in order to determine the safety and efficacy of *in situ* prosthetic repair
Methods: Data regarding the present symptoms, investigations, operative techniques and outcome were obtained from operation notes and hospital records. Seven patients were treated between 1992 and 1998.
Results: The mean age of the patient group was 62 years (range, 24–80) with median symptom duration of 11 weeks. Seventy-one per cent presented with abdominal or back pain, 29 per cent with fever and 29 per cent with an elevated white cell count, and three patients (43 per cent) were ruptured at the time of admission. Organisms identified via blood or tissue culture included coliforms, streptococci and salmonella, and no organisms were isolated in three patients CT was used to confirm the diagnosis prior to surgical repair in all cases Repair using a rifampicin-soaked Dacron prosthesis was performed in addition to extensive local debridement. There were two early deaths, one related to blood loss and the other to overwhelming sepsis. All surviving patients have been followed up for a mean duration of 46 months (range, 14–84), and only one had shown signs of septic recurrence requiring further surgical intervention with insertion of an aortic homograft.
Conclusions: In the absence of uncontrolled sepsis, infected suprarenal aortic aneurysms can be successfully repaired using *in situ* prosthetic grafts and local tissue debridement with durable intermediate results.

Vascular 019

UK talent endograft experience: current registry results

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Methods: Since 1997, 131 patients, with a median age of 73·5 years (range, 52–94) and asymptomatic AAAs, were recruited in 15 vascular centres. There were 113 males and 18 females. Indications for repair were established individually at each hospital. Endpoints included primary technical success, 30-day mortality, morbidity and reintervention for complications. Follow-up data were obtained up to 2 years (range, 6–24 months).
Results: AAA had a median maximal AP diameter of 60 (range, 38·7–92·1) mm. The proximal neck median upper and lower diameters were 24 (range, 16–34) mm and 25·4 (range, 16–36·9) mm respectively Median neck length was 26 (range, 9–60·8) mm. In a subset of 42 patients, median ITU stay was 1 day (range, 0–42) and mean ward stay was 7 days (range, 2–14). The ratio aorto-uni-iliac bifurcated grafts used was 1:4 Two grafts could not be successfully implanted owing to technical problems at deployment Thirty-day mortality was 4 per cent (5/131 patients) in the whole group. Two patients died from rupture before implantation There were five ilio-femoral arterial injuries requiring surgery and five cases of renal failure requiring active treatment One patient had graft migration causing renal occlusion and immediate conversion, and one case of late distal migration has been reported. In the subset of 42 patients, predischarge CT showed seven type I (17 per cent) but only two persisted at 6 months (5 per cent), and five type II endoleaks (12 per cent), all of which sealed spontaneously at 6 months. One persisting type I endoleak remains, and the other was sealed by endolumenal technique The median AAA volume in this group decreased from 157·5 mL (range, 122·3–409·3) to 148 mL (range, 70·2–403·0) at 6 months and to 94·9 (range, 66·0–163·0) mL at 1 year ($P<0{\cdot}02$).
Conclusions: The talent endovascular graft may be implanted with a low mortality, morbidity and favourable mid-term survival rate. Only one case of distal migration has been reported in the UK so far. No delayed ruptures or endoleaks have been reported. Long-term monitoring of all patients undergoing treatment is necessary before a verdict regarding durability can be made.

Vascular 020

Thoraco-abdominal aortic aneurysm: evaluation of preoperative assessment in 257 elective repairs

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Aims: Thoraco-abdominal aneurysm repair continues to be associated with significant postoperative mortality. We wished to review preoperative assessment in the selection of asymptomatic patients for surgery
Methods: Audit data on 257 patients who underwent elective aneurysm repair following standard preoperative assessment between June 1990 and August 1999 were analysed.
Results: Mean patient age 68 years (range, 17–83), three male, one female. Some 118 patients (45·9 per cent) presented with aneurysm-related symptoms The principal aneurysm aetiologies were atherosclerosis (215 degenerative; 21 dissected; 11 inflammatory), Marfan's (eight) and infection (two). Aneurysm extent (Crawford): I 23, II 48, III 51 and IV 133 In-hospital mortality was 26·1 per cent, with 15·2 per cent suffering transient or permanent lower-limb neurology.

Significant preoperative predictors of postoperative mortality (univariate analysis)

Variable	Group	n	Deaths	Odds ratio (95% CI)		P (χ^2)
Pulmonary function	<75% pred	66	30	4·72	(2·4–9·5)	<0·001
Aneurysm extent	II	48	21	3·32	(1·6–6·9)	0·002
	III	51	18	2·33	(1·1–4·9)	0·038
Plasma creatinine	>125 µmol L^{-1}	65	28	2·97	(1·6–5·4)	<0·001
	>175 µmol L^{-1}	16	12	3·45	(1·5–8·2)	0·008
Hypertension	yes	160	48	2·17	(1·2–4·1)	0·023

Age, symptoms, cardiac history, aortic dissection, stress echocardiography and coronary angiography did not predict poor outcome Aneurysm extent, pulmonary function, serum creatinine (log scale) and hypertension all remained significant predictors (fitted individually and jointly) on multivariate analysis
Conclusions: Cardiac morbidity does not influence outcome, possibly as a result of protocols for investigation and intervention. This study aids management in patients with extensive aneurysms, pulmonary or renal disease.

Vascular 021

Causes of recurrence after PTFE patch saphenoplasty for recurrent varicose veins: analysis by duplex imaging and varicography

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Aims: Forty-three patients who had surgery for recurrent long saphenous veins (70 legs), done or supervised by a consultant vascular surgeon, had a small PTFE patch sutured over the religated saphenofemoral junction. There were no major complications following surgery. Three patients had a wound infection or delayed healing. There have been no further groin reoperations but one patient subsequently had short saphenous ligation, one had local avulsions and one sclerotherapy. All patients had clinical examination or duplex imaging median 19 months after operation (range, 6–39).

Methods: Some 38/43 patients examined (70 legs) were satisfied with the results of their surgery. Sixteen legs (23 per cent) had visible veins on inspection, eight of these had symptomatic recurrence (11 per cent). Duplex imaging showed recurrence was caused by saphenofemoral junction incompetence in ten legs; two appeared to have a major groin connection but the other eight appeared to have neovascularization. Other causes were thigh perforator (three) and cross-groin collateral (three legs).

Results: To date, 11/16 of the legs with recurrence have had varicography. In two, the procedure was a technical failure and the remainder declined. Two legs had evidence of a significant, and two a minor connection to the femoral vein at the level of the patch but, in the remainder, recurrence was caused by thigh-perforating veins There was reasonable concordance between duplex and varicography, but duplex tended to overdiagnose connections at the saphenofemoral junction.

Conclusions: This pilot study of PTFE saphenoplasty has shown it to be safe. Although these are early results, the technique seems potentially as effective as other barrier methods that have been investigated; in only four legs (6 per cent) can recurrence be attributed to failure at the level of the patch

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Vascular 022

Subfascial endoscopic perforator surgery (SEPS): an observational study in 61 consecutive patients

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Aims: To investigate the outcome of subfascial endoscopic division of incompetent perforating veins.

Methods: Patients with incompetent perforating veins, determined by Duplex scanning or phlebography, with signs of advanced lipodermatosclerosis (LDS) and venous ulceration were recruited during the period between December 1996 and October 1999

Results: There were 21 males and 40 females with an average age of 63·3 and 66·4 years respectively. Of the sixty-one patients, 25 had ulcers and the remaining 36 patients had advanced skin changes All the ulcerated limbs were already being treated by compression therapy. There were 33 patients who previously had junctional surgery (27 SFJ and six SPJ). Only three patients had evidence of deep venous reflux. There were five patients with isolated perforator veins incompetence The SFJ was incompetent in 25 patients and the SPJ was incompetent in four patients Of these patients, five required redo surgery The follow-up period ranged from three to 18 months Two patients died during the follow-up period and two others were lost to follow-up. The ulcers healed in 15 patients, improved in seven and remained unhealed in two patients. The skin changes improved in 28 patients and remained unchanged in eight patients One patient with refractory ulcer and four patients with persistent skin changes had redo SEPS for missed perforators with good results The early complications included wound infection (three), haematoma (three), tunnel infection (two) and swelling (two). The late complications were transient paraesthesia (nine) and permanent paraesthesia (two). The average hospital stay was 2·4 days.

Conclusions: SEPS is effective in the treatment of patients with ulceration and preulcerated limbs with evidence of incompetent perforating veins. Its long term benefit remains to be determined

Endocrine

Poster 001

Laparoscopic adrenalectomy: prospective follow-up of 34 patients

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Aims: This is a prospective follow-up of 40 consecutive laparoscopic adrenalectomies in 34 patients performed by one consultant in the past 6 years.
Methods: All patients from September 1993, who underwent laparoscopic adrenalectomy by one surgeon, were included in the study Data were recorded prospectively at operation, and supplemented after discharge by postal follow-up in patients from other institutions, and review at 4–6 weeks in the outpatient's clinic.
Results: Thirty-four patients (23 female patients) underwent 40 adrenal resections, 13 left, 15 right and six bilateral The diagnoses included Cushing's disease ($n=9$), Conn's syndrome ($n=7$), phaeochromocytoma ($n=8$) and 10 miscellaneous conditions. The mean operating time was 122 min per gland (range, 40–225 min), laparoscopic cholecystectomy was performed concurrently in four patients; there were no conversions to open surgery. There were three early postoperative complications, including a pancreatic fistula (managed conservatively), a port-site hernia (repaired under local anaesthesia) and a port-site infection The median length of stay was 3 days; range, 1–16 (average = 4·6).
Conclusions: Laparoscopic adrenalectomy can be performed safely, with a zero conversion rate, in the majority of patients. Inpatient stay is reduced compared with the open procedure.

Breast

Poster 002

Magnetic resonance imaging as an adjunct to triple assessment in equivocal breast disease

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Aims: The process of triple assessment, which comprises clinical examination, imaging with mammography and ultrasound and cytopathological analysis, will determine the nature of most breast abnormalities. The aim of this study was to determine whether the availability of breast MRI provides additional helpful diagnostic information
Methods: T2 weighted turbospin echo plus two-dimensional gradient echodynamic breast scanning with gadolinium was performed on 100 patients where there was diagnostic uncertainty following triple assessment All scans were assessed by a dedicated breast radiologist Indications included confirmation of malignancy (21), determination of extent of probable multifocal disease (15), assessment following previous surgery (39), assessment of primary distortion (11), elucidation of primary carcinoma in axillary lymphadenopathy (four), monitoring response to neoadjuvant chemotherapy (six)
Results: The median age was 54 years (range, 27–79). MRI correctly identified carcinoma in all 47 patients with malignancy (sensitivity, 100 per cent). Fifty of 53 patients without malignancy were correctly identified (specificity, 94 per cent) Two false positives were inpatients with duct ectasia. MRI identified two cases of lobular carcinoma where previous radiology had been benign
Conclusions: MRI is a useful adjunct, rather than a replacement for triple assessment in breast disease. It is particularly helpful in detecting lobular carcinoma and assessing the extent of multifocal disease

Poster 003

Does routine grading of invasive lobular cancer of the breast have same prognostic significance as for ductal cancers?

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Aims: The routine tumour grading of invasive ductal carcinoma of the breast has been shown to be a robust determinant of outcome. However, pathologists have been reluctant to grade lobular cancers and the aim of this study was to determine the prognostic significance of routine reporting of lobular grade (G)
Methods: All invasive lobular cancers (ILCs) treated between 1981 and 1996 were reviewed Patients were case-matched with two control patients with invasive ductal carcinoma (IDC) who were operated in the same year and were nearest in age Recurrence-free survival was compared with grade for ILC cases and IDC controls.
Results: Out of 139 cases with ILC, 33 were excluded from the study; 24 were ungraded, five had advanced disease and four had mixed tumours. The mean length of follow-up for ILC was 75 *versus* 70 months for IDC. Recurrence rates are shown in the table.

Grade	Lobular	Ductal
Grade I	4/40 (10%)	17/71 (24%)
Grade II	19/60 (32%)	27/84 (32%)
Grade III	2/6 (33%)	28/57 (49%)

Kaplan–Meier recurrence-free survival Log-rank ILC GI *versus* GII $P=0{\cdot}01$, IDC GI *versus* G II $P<0{\cdot}6$, GII *versus* GIII $P<0{\cdot}02$

The reported grades of ILC and IDC show the expected trend for an increased recurrence rate with more severe tumour grade but, for ILC, this was not significant on life table analysis; only 6 per cent of patients were reported grade III.
Conclusions: The routine reporting of tumour grade for ILC did not show a significant difference in outcome between grade I and grade II, and very few tumours were rated grade III. The validity of grading lobular cancer of the breast requires further evaluation

Poster 004

Targeted intraoperative radiotherapy (TARGIT): a novel approach to local treatment of early breast cancer

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Aims: We believe that conservative treatment of breast cancer does not require radiotherapy that encompasses the whole breast We present here the clinicopathological basis for this belief and a novel therapeutic approach that allows intraoperative radiotherapy to be safely and accurately delivered to the target tissues in a standard operating theatre
Methods: *The rationale.* Whole-organ analysis of mastectomy specimens reveals that 80 per cent of occult cancer foci are situated remote from the index quadrant. In contrast, over 90 per cent of local recurrences after breast conservative therapy occur near the original tumour – whether or not radiotherapy is given and whether or not the margins are involved. Therefore, these occult cancer foci may be clinically irrelevant and radiotherapy to the index quadrant alone might be enough *A novel technique.* The photon radiosurgery system (PRS) is an ingenious portable electron-beam-driven device that can deliver therapeutic radiation intraoperatively Being soft X-rays, the dose rapidly attenuates ($\alpha \sim 1/r^3$), reducing distant damage In about 25 min 5–20 Gy can be delivered, respectively, to 1 cm and 0·2 cm from the tumour bed. The pliable breast tissue – the target – wraps around the source, providing perfect conformal radiotherapy

Results: In our pilot study of 23 patients, we replaced the routine postoperative tumour bed boost with TARGIT. The age ranged from 30 to 80 years and tumours from 0·42 to 2·5 cm There have been no major complications. The cosmetic outcome has been good to excellent and no patient has developed local recurrence at the median follow-up of 7 months

Conclusions: It is safe and feasible to deliver TARGIT for early breast cancer We have submitted a proposal for a randomized trial comparing conventional radiotherapy with TARGIT with a potential elimination of conventional postoperative radiotherapy.

Poster 005

Outcome of treatment in 355 cases of pure ductal carcinoma *in situ* of the breast

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Aims: The incidence of ductal carcinoma *in situ* (DCIS) has dramatically changed since the advent of mammographic screening This study evaluated the outcome of different treatments.

Methods: We reviewed 355 patients with pure DCIS (without invasion) seen in Merseyside between 1989 and 1999.

Results: Patients had a mean age of 57 years (range, 35–83) and mean follow-up of 51 months (range, 1–252).

Treatment	WLE	WLE/T	WLE/R	WLE/T/R	M	M/T	Total
Number	57	115	8	26	68	82	355
Recur							
DCIS no (%)	10 (17·5)	10 (8·7)	–	–	0 (0)	–	20
Invasive no (%)	6 (10·5)	4 (3·3)	–	–	2 (3)	–	12
Total Recur no (%)	16 (28)	14 (12)	0 (0)	0 (0)	2 (3)	0 (0)	32

Abbreviations wide local excision (WLE), Tamoxifen (T), radiation (R), mastectomy (M), recurrence (Recur), number (no)

Of the 32 recurrences, 12 (37·5 per cent) were invasive of which three had regional nodal involvement and one had bone marrow involvement. In addition, there were eight cases of contralateral breast cancers of which half were invasive None of those patients with adjuvant Tamoxifen treatment developed contralateral carcinoma.

Conclusions: In this series, wide local excision alone is associated with a high risk of recurrence (28 per cent) This rate is reduced by Tamoxifen and radiotherapy (although the numbers are small) Tamoxifen also reduces the incidence of contralateral cancers.

Poster 006

Wolfe mammographic patterns and breast cancer risk: a prospective study

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Aims: To evaluate the risk of breast cancer with respect to mammographic density as described by Wolfe who classified the mammograms into N1, P1 codes (less density) and P2 and DY codes (increased density)

Methods: In 1980, a prospective study of symptomatic breast patients, attending the breast clinic, was set up to determine whether patients with Wolfe code P2 or DY had a higher risk of developing breast cancer than those with N1 or P1 codes. A total of 5021 women between 1980 and 1985 had their mammograms coded according to Wolfe classification. We present our interim results of the analysis of this cohort From the pathology records of the hospital and crematorium records from the district crematorium, we have matched the cases that had a diagnosis of breast cancer with our cohort to identify patients who developed interval breast cancer.

Results: We have identified a total of 280 patients in the initial cohort who have developed breast cancer The distribution of these patients according to Wolfe coding was as follows. N1 = 42, P1 = 51, P2 = 143, DY = 44. The overall proportion of low-risk codes (N1 and P1) was 33 per cent and that of high-risk codes (P2 and DY) was 67 per cent The proportion of these codes in the overall sample of 5001 evaluable patients was 51 per cent and 49 per cent respectively. This difference was statistically significant

Conclusions: The interim results are in line with the earlier reports that high-density Wolfe coding increased the risk of breast cancer

Poster 007

Sentinel lymph node in breast cancer: lessons learnt

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Aims: It has been suggested that sentinel lymph node (SLN) biopsy is an accurate, minimally invasive technique for staging the axilla in breast cancer, although there is no consensus on the optimal method of lymphatic mapping. This study aimed to examine two techniques of lymphatic mapping and determine the feasibility in patients with impalpable breast cancers

Methods: Lymphatic mapping was carried out in 71 patients with palpable breast cancers using patent blue dye alone Based on the results of this study, SLN biopsy was carried out using a combination of patent blue dye and radioisotope in a further 70 patients with tumours 30 mm or less in diameter on ultrasound (both palpable and impalpable). Where feasible, preoperative lymphoscintigraphy was carried out and the operating surgeon blinded to the result.

Results: The use of patent blue dye alone allowed identification of the SLN in 69 per cent of patients, with a false-negative rate of 16 per cent and a mean time to SLN excision of 15·1 min. The combined technique yielded an SLN detection rate of 96 per cent with a false-negative rate of 0 per cent and a mean time to SLN excision of 7·9 min. The use of lymphoscintigraphy did not affect the rate of SLN identification There was no difference in SLN identification rate in palpable and impalpable tumours,

Conclusions: The use of a combination of patent blue dye and radioisotope appears to be the optimal method for lymphatic mapping and SLN biopsy in breast cancer, and this technique appears applicable in both palpable and impalpable cancers. The use of lymphoscintigraphy does not appear to increase the accuracy of the technique in this study

Poster 008

Sentinel node biopsy: the way ahead for small breast cancers

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Aims: The majority of patients with T1 breast cancers will be axillary node negative. We have performed a prospective study to assess whether sentinel node biopsy can accurately stage the axilla in patients with T1 tumours, so avoiding the morbidity of a full axillary clearance.

Methods: The sentinel node was identified with a combination of radionuclide and blue dye. 10–40 MBq Tc^{99m} labelled human colloidal albumin was injected peritumourally, 2·5–24 h preoperatively. Two mL patent blue dye were injected peritumourally, 5 min preoperatively. A hand-held gamma probe was used to help identify the sentinel node. The patient then underwent mastectomy or wide local excision and axillary clearance or sampling.
Results: Seventy patients with a mean age of 57·9 years and a mean tumour size of 13·8 mm underwent sentinel node biopsy. A mean of 1·8 sentinel nodes were found per patient. The sentinel node was found in 68/70 (97·1 per cent) cases and predicted axillary status in 67/68 (98·5 per cent) cases. The sentinel node was involved by a metastasis in 20/68 (29·4 per cent) cases and was the only involved node in 12 cases. In three of these cases, the metastasis was less than 2 mm in diameter.
Conclusions: In patients with T1 tumours, sentinel node biopsy allows accurate determination of axillary status.

Poster 009

Ten years' experience of complex sclerosing lesions: high risk of associated malignancy

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Aims: To review association of radial scar/complex sclerosing lesions (RS/CSLs) and cancer. To identify features on mammography that would distinguish RS/CSLs associated with cancer from those not so associated.
Methods: Retrospective review of 10 years' screening and symptomatic detected RS/CSLs. All histologically proven RS/CSLs were entered on a database. Pathology slides were reviewed by one breast histopathologist, and mammograms were reviewed by one of three breast radiologists. Those associated with malignancy and those not so associated were compared.
Results: Ninety-five RS/CSLs were diagnosed in 90 patients between March 1990 and May 1999. Thirty RS/CSLs (32 per cent) were associated with carcinomas, half of which were invasive (10 invasive ductal carcinoma, four invasive tubular carcinoma), one invasive lobular carcinoma, 14 ductal carcinoma *in situ*, one lobular carcinoma *in situ*). Mammographic features of these lesions were no different between the two groups.
Conclusions: RS/CSLs are frequently associated with malignant, but mammographic features do not help distinguish the malignant associated and nonassociated groups. This study supports the widely held view that all RS/CSLs should be excised.

UGI

Poster 010

Preoperative chemotherapy and radiotherapy, plus excision (CARE) for locally advanced oesophageal carcinoma: a Phase II study

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Aims: To optimize the chemoradiotherapy and surgical programme for patients with locally advanced oesophageal carcinoma.
Methods: Thirty-three patients, median age 60 years (31–70 years), with T3 tumour of the oesophagus (25 adenocarcinoma and eight squamous carcinoma), staged by means of EUS and spiral CT, were treated with protracted venous 5FU infusion (300 $mg\,m^{-2}\,day^{-1}$ d1–42, 225 $mg\,m^{-2}\,day^{-1}$ d43–75) and Cisplatin (60 $mg\,m^{-2}$ d1, 22, 43, 64) along with concurrent radiotherapy (45 Gy, d43–75, in 25 daily fractions). Radical oesophageal resection with two-field lymphadenectomy was planned 6 weeks after completion of chemoradiotherapy.
Results: Of the 33 patients entered into the study so far, 18 have undergone oesophageal resection with one postoperative death (6 per cent); six of the 18 (33 per cent) had complete pathological response and a further 10 (56 per cent) had significant downstaging of the tumour. With median follow-up of 10 months from resection (0–17 months), only one patient has relapsed and died. There were two treatment related deaths (one line-related SVC thrombosis and one unrelated perforation of sigmoid diverticular disease). Grade III toxicity was reported in 19 of the 33 patients treated (57 per cent) and this resulted in dose-reduction of chemotherapy in 11 patients (33 per cent).
Conclusions: The CARE programme produces a high rate of downstaging and pathological response in patients with locally advanced oesophageal carcinoma, although there was quite significant chemotherapy toxicity. This regimen may be suitable for use in future Phase III trials.

Poster 011

Laparoscopic splenectomy: an early experience

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Aims: To evaluate and analyse our initial experience of laparoscopic splenectomy.
Methods: Between January 1989 and October 1999, 21 patients underwent elective laparoscopic splenectomy for haematological disorders and suspected malignancy. All were performed in the right anterolateral position. The technique has evolved. We now use the harmonic scalpel for short gastric vessels division (16 patients) and ligate the hilum with an endoscopic stapler (14 patients). Indication, splenic size, operative time, blood loss, perioperative morbidity and hospital stay were analysed.
Results: The mean age of the patient was 40 years (16–78). M:F = 1:2. Splenectomy was for idiopathic thrombocytopenic purpura (10), haemolytic anaemia (eight) and suspected lymphoma (three). In three cases, accessory spleens were identified and removed. Mean operative time was 102 min (range, 45–160) and was related to the size of the spleen. All these specimens were retrieved in a bag using morcellation – a technique which has also evolved. The maximum size retrieved successfully was 20 cm (CT measurement). No patients required conversion. Four (20 per cent) patients required blood transfusion. Median hospital stay was 4 days (IQR, 2–7). Morbidity was 14 per cent. Complications included one bleeding from short gastric vessels that required laparotomy, one patient had port-site breakdown and one had delayed gastric greater curve perforation, possibly secondary to thermal injury. There was no death.
Conclusions: Laparoscopic splenectomy is a technically feasible option in haematological disorders with short recovery time. Complications do occur but can be minimized by attention to surgical technique.

Poster 012

Magenstrasse and Mill vertical gastric stapling for morbid obesity

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Aims: To determine the effects of a new, vertical gastric stapling procedure used alone or in combination with a Roux-en-Y gastric bypass for patients with morbid obesity.
Methods: A consecutive series of 100 patients with morbid obesity underwent either vertical gastric stapling alone (Magenstrasse and Mill

procedure) ($n=80$) or combined with a limited Roux-en-Y gastric bypass ($n=20$). The median age (39 *versus* 40 years), BMI (45·9 *versus* 45·8) and male female ratio (1:4 *versus* 1:3) were similar between the two groups of patients. The median follow-up of the patients who underwent the M&M procedure was 36 months (0–72 months) and it was 15 months (0–36 months) for patients who had the combined M&M and gastric bypass procedure.

Results: Operative mortality was 0 per cent and there were no major postoperative complications. Median length of stay was 7 days for patients who had the M&M procedure and 10 days for patients who underwent combined M&M–GB procedure. One year after operation, median (s.d.) weight loss was 38·6 (15 1) kg in the M&M group against 50 4 (8 4) kg in the M&M–GB group ($P=0{\cdot}02$) The patients who had the M&M procedure had lost 30 (8·3) per cent of their original weight compared with 36 (3·2) per cent for patients who had a combined M&M–GB procedure ($P=0{\cdot}03$)

Conclusions: Gastric stapling for morbid obesity is safe in specialized surgical units Weight loss after the combined M&M–GB procedure was greater than that of the M&M procedure alone, although this has to be set against the potential long-term complications of a gastric bypass procedure

Poster 013

Morbidity and mortality after surgery for oesophagogastric malignancies – the value of a risk stratification system

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Aims: Radical surgery for oesophagogastric cancer carries some of the highest hospital mortality for elective operations. These mortality rates vary widely and are often used as comparative measures between different centres without description of confounding factors such as comorbid disease and/or stage The aim of this study was to use a validated risk stratification system (POSSUM and p-POSSUM) to assess whether predicted mortality and morbidity correlated with actual mortality and morbidity.

Methods: Ninety consecutive patients (60 oesophagectomy, 30 D2 gastrectomy) undergoing radical surgery with curative intent were scored using POSSUM and p-POSSUM. Postoperative morbidity and mortality were recorded

Results:

Number of resections	Predicted morbidity	Actual morbidity	Predicted mortality	Actual mortality
90	63 2%	60 2%	6 5%	6 8%

Conclusions: POSSUM and p-POSSUM are easy to use, and accurately predict the overall incidences of morbidity and mortality in radical surgery for both oesophageal and gastric malignancies. Risk stratification should be included in descriptions of surgical series, so that comparisons between different centres can be meaningful.

Poster 014

COX-2 expression in Barrett's oesophagus, dysplasia and adenocarcinoma

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Aims: Increased expression of the inducible cyclo-oxygenase 2 (COX-2) enzyme has been detected in oesophageal and colonic adenocarcinoma, and inhibition has been shown to decrease colonic adenoma/carcinoma formation. Elevated COX-2 mRNA but variable protein expression has been demonstrated in Barrett's epithelium, so we have sought to evaluate the expression of COX-2 protein throughout the Barrett's metaplasia–dysplasia–carcinoma sequence

Methods: Fifty-six paraffin-embedded oesophageal biopsies from different patients with Barrett's oesophagus were analysed for COX-2 expression by immunohistochemistry. Twenty contained nondysplastic intestinal and gastric metaplasia, 12 showed low-grade dysplasia (LGD), 12 showed high-grade dysplasia (HGD) and 12 contained invasive adenocarcinoma.

Results: Epithelial expression of COX-2 protein was detected in 75 per cent (15/20) of benign cases, 83 per cent (10/12) of cases with LGD and 100 per cent of cases with HGD or adenocarcinoma. Using a semiquantitative analysis, median staining scores for the groups were 2, 3, 14 and 13 respectively (scale, 0–16), with the expression being significantly higher in the HGD and cancer groups compared with benign and LGD groups ($P<0{\cdot}001$). Three patients in the benign/LGD groups demonstrated dense focal expression.

Conclusions: Frequent weak expression of inducible COX-2 enzyme is demonstrated in benign Barrett's epithelium, with significantly higher expression in high-grade dysplasia and oesophageal adenocarcinoma The benign/LGD subgroup with higher COX-2 expression may represent tissues early in the process of malignant transformation.

Poster 015

Alterations in serum lymphocyte and plasma amino acid profile following radical oesophagectomy and gastrectomy

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Aims: The immunological response to major oncological surgery is poorly understood. The aim of this study was to evaluate alterations in the levels of various lymphocyte phenotypes and their relationship to plasma amino acid levels following radical resection for oesophageal and gastric cancer

Methods: Eleven consecutive patients undergoing oesophagectomy ($n=6$) and D2 total gastrectomy ($n=5$) from January to March 1999 were studied Preoperative baseline measurement was followed by serial postoperative assay of 22 plasma amino acids and lymphocyte subsets on days 1–14 Amino acids were assayed with high-performance liquid chromatography and lymphocyte counts analysed by fluorescence-activated cell sorter scanner

Results: Decreases in the expression of T-CD3, T-CD4, T-CD8, BCD19 and total NK-CD16+/56+ were observed in all 11 patients. Among all amino acids analysed, only plasma glutamine levels fell significantly ($P=0{\cdot}004$). The drop in plasma glutamine levels correlated with the depression in the levels of all lymphocyte subsets: T-CD3. r (correlation coefficient) = 0 98, $P<0{\cdot}01$; total NK $r=0{\cdot}97$, $P<0$ 01; B-CD19 $r=0{\cdot}84$, $P<0$ 05; T-CD4 $r=0{\cdot}95$, $P<0{\cdot}01$, and T-CD8 $r=0$ 94, $P<0{\cdot}01$. In 18 per cent (2/11) of patients, the CD4/CD8 ratio was reversed and both patients had evidence of tumour disruption with a peritumoral sterile abscess found at the time of surgery. The mean plasma glutamine levels in these patients were significantly lower ($P=0{\cdot}003$) when compared with others. The changes in both lymphocyte subset counts and amino acid levels were comparable for both gastrectomy and oesophagectomy groups

Conclusions: Glutamine levels decrease in concordance with falls in all lymphocyte subset cell counts, with significantly lower levels in relation to profound immunodeficiency (reversal of CD4/CD8 ratio) A randomized, controlled trial is required to determine the potential benefits of glutamine supplementation following major upper gastrointestinal cancer surgery

Posters 016

The role of positron emission tomography in the detection of recurrent and metastatic colorectal cancer

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Aims: This study was performed to establish the clinical role of positron emission tomography (PET) with fluorodeoxyglucose (FDG) compared with computed tomography (CT) and magnetic resonance imaging (MRI) in the detection of suspected recurrent or metastatic colorectal cancer.
Methods: A retrospective study of 32 patients recurrent PET for the evaluation of suspected recurrent or metastatic colorectal cancer over a 3-year period PET results were compared with corresponding CT and, in 13 cases, MRI reports and correlated with operative findings or clinical course.
Results: The indications for PET were (1) inconclusive CT scans (56 per cent); (2) increasing CEA and negative CT scan (31 per cent), (3) clinical suspicion with normal investigations (13 per cent). Twenty-nine of 32 patients were confirmed to have recurrent disease by laparotomy or clinical progression Recurrence was either local, hepatic, extrahepatic or any combination of these PET was a more sensitive investigation than CT and also MRI in detecting local disease (Table) The specificities of PET, CT and MRI in this series were 100 per cent in all cases.

Sensitivities	Local	Hepatic	Extrahepatic
PET	87%	94%	75%
CT	80%	59%	50%
MRI	50%	100%	

Conclusions: In this series, PET is a more sensitive investigation than CT in assessment of patients with suspected recurrent or metastatic colorectal cancer. A PET scan should, therefore, be considered if biochemical indicators or clinical suspicion suggest recurrence in the absence of CT findings

Poster 017

P53 positive colorectal carcinomas overexpress BCL2

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Aims: This study investigated coexpression of P53 and BCL2 in CRC (colorectal carcinoma), and association of these oncoproteins with survival characteristics following a curative resection.
Methods: Sections of curatively resected CRC were examined by immunohistochemistry for expression of P53 and BCL2 oncoproteins Survival rates were computed by the Kaplan–Meier method
Results: Sections from 11 TNM stage I, 28 stage II and 26 stage III CRC were studied The prevalence of BCL2 overexpression was significantly greater in P53+ tumours as compared with P53– tumours (60·5 per cent *versus* 31·8 per cent respectively, $P=0·03$). Tumours were assigned one of four immunophenotypes. P53–/BCL2– (15/65; 23·0 per cent), P53+/BCL2– (17/65, 26·2 per cent), P53–/BCL2+ (7/65; 10·8 per cent) and P53+/BCL2+ (26/65; 40·0 per cent). As expected, the 5-year survival rate of patients with stages I and II CRC was significantly higher than that of patients with stage III CRC ($P=0·03$) However, further stratification according to tumour immunophenotype failed to identify subgroups of patients with significantly altered survival characteristics.
Conclusions: Cosegregation of tumours immunopositive for mutant P53 and BCL2 implies that mutations in P53 may result in failure of regulation, with consequent overexpression of BCL2 The clinical significance of this phenomenon, however, remains unclear.

Poster 018

Family history of HNPCC-spectrum cancer is associated with deficient mismatch repair

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Aims: Abnormality of mismatch repair (MMR), typical of hereditary nonpolyposis colorectal cancer (HNPCC), is also found in colorectal cancer (CRC) derived from the general population. This study investigates MMR deficiency as a possible mechanism for familial clustering of CRC.
Methods: Cancer tissue from 416 individuals with CRC identified from a single surgical practice was stained using an immunohistochemical technique for the MMR genes hMLH1 and hMSH2. MMR expression was related to family history of cancer.
Results: Forty-six cancers exhibited MMR deficiency (11 per cent). There was no association between MMR deficiency and family history of CRC ($P=0·2$). However, a family history of extracolonic HNPCC-spectrum cancer was associated with increased loss of expression (LOE) of MLH1 and MSH2 (24 per cent) compared with patients with no family history (10·6 per cent, $P=0·03$) LOE was also more common than when compared with a family history of CRC alone (24 per cent *versus* 7·4 per cent, $P=0·01$).
Conclusions: MMR deficiency is seen more frequently in CRC cases associated with a family history of extracolonic cancer than those with a family history of CRC alone. These results suggest that clustering of HNPCC-spectrum cancers is related to deficiency of mismatch repair, and families affected by both CRC and extracolonic cancer may harbour an inherited MMR gene abnormality

Poster 019

Symptomatology and fibre intake in patients with diverticular disease

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Aims: To study the bowel habit of patients with diverticular disease and the effect of dietary fibre on their symptoms.
Methods: A questionnaire regarding episodes of abdominal pain, normal bowel habit (IBS symptoms, Rome 1 criteria) and diet was sent to 379 patients with diverticular diagnosed on barium enema
Results: Median (range) 68·9 per cent completed questionnaires, 55 per cent female, age 69 years (36–91). Only 59 (22·6 per cent) patients were asymptomatic. Two types of pain were defined, type 1 lasting more than 24 h and type 2, recurrent abdominal pain of less than 24 h duration. Type 1 51 (19·5 per cent) patients reported bouts of type 1 pain Median duration of the longest attack was 3 days (1–60) (IQR, 2–5) The frequency of defaecation during the attacks was twice per day (0·5–6) and 37/51 (72·5 per cent) passed altered stool (watery 49 per cent, hard 59 per cent, 35 per cent both) Thirty-two patients (62·8 per cent) had sought emergency medical attention and 50 per cent had been prescribed antibiotics Type 2: 94/261 (36 per cent) experienced type 2 pain, with a median frequency of 5 days per month (0·3–31) (IQR, 2–13). Median duration of pain was 3 h (0·1–12) and frequency of defaecation of this group was once per day (0·3–5). Fifty-three per cent of patients met Rome 1 IBS criteria 23/51 (45·1 per cent) of patients with type 1 pain and 45/94 (49·5 per cent) with type 2 pain said their symptoms became worse by eating a high fibre diet (χ^2 14·5 and 26·7, d.f 1, $P<0·005$ and $P<0·0001$ respectively).
Conclusions: Patients with diverticular disease report a high incidence of gastrointestinal symptoms Although a lack of dietary fibre may result in disease progression and complications, introduction of high-fibre foods may worsen the symptoms of a significant proportion of patients

Poster 020

Clinical response of ulcerative colitis with dietary omega-3 fatty acids: a double-blind randomized study

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Aims: In this double-blind randomized study, patients with active and extensive colitis, not previously treated with immunosuppressants, were studied and the clinical efficacy of EFAs was evaluated.
Methods: Patients ($n=51$) receiving standard therapy, were randomized to receive either placebo (sunflower oil) or dietary supplementation with omega-3 EFAs (5·6 mg day^{-1}) for 6 months. Patients were assessed prior to commencement of therapy, 3 months later and at the end of the study period (6 months). Extent of disease, colonoscopy (1–7) and clinical (1–32) scores were used to assess the severity of the disease
Results: There was disease improvement in both groups of patients but this was more significant in the group receiving the EFAs In particular, there was significant improvement in the clinical ($P=0·001$) and colonscopic ($P=0·054$) scores in the EFA group ($n=21$). Dietary supplementation with EFAs was well tolerated and produced minimal side effects
Conclusions: In order to improve on present immunosuppressive therapy, nontissue damaging therapy needs to be introduced and EFAs may be such a promising approach to control this difficult-to-treat disease. This study has important implications for managing patients with ulcerative colitis.

Poster 021

Anorectal fistulas in Crohn's disease: a plea for conservative management

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Aims: Anorectal sepsis and fistulas are common in Crohn's disease (CD) and cause intermittent symptoms but rarely incontinence
Methods: We have examined the impact of anorectal fistulas on the surgical treatment of CD from our database of 750 patients
Results: Overall 199 of 750 patients (27 per cent) have had intermittent symptoms from perianal fistulas. To date, 268 have had a rectal excision, of whom 122 (46 per cent) had an anorectal fistula. The fistula was rarely responsible for the proctocolectomy. Only 77 of 483 patients (16 per cent) with an intact anorectum have an anorectal fistula. Of these, 60 (78 per cent) are quiescent and only 17 (22 per cent) are active Detailed study of the 17 active anorectal fistulas revealed that eight had been treated by seton and nine by a lay-open procedure Using the Cleveland Clinic incontinence score, overall continence was compromised by operation; preoperative 4·8, postoperative 7·9; $P=0·00029$. When a seton was used there was no change in continence scores (preop. 4·8; postop 5·1; not significant), whereas in those managed by lay-open, continence scores fell significantly (preop. 5·1, postop. 9·6; $P=0·0007$).
Conclusions: Anorectal fistulas are more common in patients requiring rectal excision Seton drainage does not compromise continence, whereas lay-open procedures may.

Poster 022

Virtual colonoscopy: experience with two-dimensional and endoluminal three-dimensional CT assessment of colorectal cancer

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Aims: Virtual colonoscopy (VC) allows endoluminal fly-through views of the colon to be reconstructed from standard two-dimensional CT images and is advocated as a potential screening tool for colorectal cancer.
Methods: We performed VC on 20 patients using full-bowel prep, colonic insufflation and two-dimensional spiral CT acquisition. 'Voyager' software was used to create the three-dimensional view Correlation is made with colonoscopy or barium enema findings and final histology.
Results: The procedure took a median of 20 (range, 15–30) min with median scan time of 2 min. All patients tolerated the procedure with Buscopan analgesia VC correctly identified all 12 cancers and visualized the proximal colon in five of these which were impassable endoscopically. VC identified two tumours in patients who had failed attempts at colonoscopy and identified four patients as having normal colons following failed/refusal endoscopy. One intramural lipoma was correctly identified on VC. However, one was not seen on VC following colonoscopic visualization. Additional polyps (remaining after the prior 'therapeutic' colonoscopy) were identified in two patients
Conclusions: Early experience with VC suggests that it has a role to play in the detection of neoplasia and also when colonoscopy has been incomplete or has failed

Poster 023

Prospective evaluation of the introduction of circumferential stapled anoplasty in the management of haemorrhoids and mucosal prolapse

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Aims: Conventional treatment of prolapsing haemorrhoids and mucosal prolapse is by variations of the ligation-excision technique, with postoperative complications often resulting in prolonged inpatient stay. This study evaluates the introduction of a submucosal resection anoplasty technique using a circular stapling device in patients requiring surgery for haemorrhoids or mucosal prolapse, assessing the suitability of this technique for day-case surgery
Methods: Patients requiring surgery for haemorrhoids (grade III ($n=26$), grade IV ($n=18$) or mucosal prolapse ($n=3$)) were eligible following appropriate investigation and informed consent Dominant symptoms included bleeding in 22 (47 per cent) and mucus discharge in 11 (23 per cent) Twenty (43 per cent) patients had previously undergone treatment for haemorrhoids, most commonly injection sclerotherapy (13 (65 per cent))
Results: Forty-seven stapled anoplasty procedures were carried out in 45 patients (25 males, median age 50 (range, 29–84) years). Excision doughnuts were complete in 46 (98 per cent) cases. Of 31 (66 per cent) patients eligible for day surgery, 23 (74 per cent) were discharged the same day Reasons for delayed discharge included pain (five cases), urine retention (two) and nausea (one). Of the whole series, 17 (36 per cent) patients were discharged the following postoperative day. Histopathological examination of the excision doughnuts was performed as a quality control measure in 20 (43 per cent), confirming haemorrhoidal tissue with no evidence of smooth muscle in all cases. Visual analogue pain score (0–10) on discharge was 1 (0–2)*. One patient was readmitted with severe anal pain and spasm. Forty (89 per cent) patients were seen at 8

weeks (21 (47 per cent) at 6 months) with 35 (88 per cent) satisfied with the results of the procedure. Objective symptom scores were 6 (4·5–8)* preoperatively and 1 (0–1)* postoperatively, $P<0·001^{\#}$. Median time to return to normal activity was 4 (2–7)* days. Two patients required repeat stapled anoplasty for residual haemorrhoids. A further two patients required proctoscopic dilation of minor staple line stenoses. No major complications were observed in this series.

Conclusions: Circumferential stapled anoplasty achieves good functional results and patient satisfaction in the surgical management of haemorrhoids and mucosal prolapse, and can feasibly be carried out as a day-case procedure. Although initial experience of this innovative technique in clinical practice is encouraging, it requires full evaluation within the confines of randomized controlled trials.

*Median (IQR) #Wilcoxon rank test.

Poster 024

Abstract withdrawn

Poster 025

Marcon tube decompression of acute colonic pseudo-obstruction

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Aims: Marcon tube placement may prevent recurrence following colonscopic decompression for acute colonic pseudo-obstruction. We studied the effectiveness of colonscopic decompression with Marcon tube placement.

Methods: Over an 18-month period, 13 consecutive patients, median age 62 years (range, 31–74), were referred with acute colonic pseudo-obstruction. The diagnosis was confirmed on plain radiology and, in every case, the caecal diameter was over 10 cm. Colonoscopy was routinely performed to exclude obstructing lesions and to provide immediate colonic decompression. In each case, a Marcon tube with a 1·1 mm internal diameter was placed over a guide wire to the ascending colon and was left in place for 3–5 days.

Results: Twelve of the 13 (92 per cent) remaining cases had resolution of the pseudo-obstruction as assessed by caecal diameter and normal bowel function. In one patient, decompression failed, neostigmine was contra-indicated, and right hemicolectomy was required. There was no mortality or complications related to the procedures. At median 12 months follow-up (range, 4–18), two patients have died and there has been no incidence of recurrent pseudo-obstruction.

Conclusions: Colonscopic decompression with Marcon tube insertion is a safe and effective treatment of acute colonic pseudo-obstruction. The Marcon tube arbitrates against the high recurrence rates described in other colonscopic decompression series.

Poster 026

Is V-Y island advancement flap suitable in the surgical treatment of chronic anal fissures?

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Aims: Despite initial enthusiasm, the use of nitric-oxide donor ointments in the treatment of anal fissures has not been a complete panacea and surgical intervention is often still required in these cases. We evaluated our own experience in the use of V-Y anal flap advancement in the treatment of chronic anal fissure.

Methods: We assessed 30 patients (24 female), aged between 22 and 80 years. The minimum follow-up was 3 months.

Results: Twenty had a posterior fissure and 10 were anterior. Duration of symptoms ranged from 2 to 36 months. Seventy per cent of patients had received GTN-based treatment. Twelve patients had previous perianal surgery (anal dilatation (one), lateral sphincterotomy (LS) (six), haemorrhoidectomy (five)). Anorectal physiology (eight) and endoanal ultrasound (six) was carried out in those patients in whom sphincter integrity was of concern. In 21 patients (19 female) the fissure was healed at 3 months. The procedure failed in four patients (two subsequently had successful LS) and five await review. Postoperative morbidity included perianal pain (eight) and minor bleeding (five). Eighteen patients (60 per cent) expressed complete satisfaction.

Conclusions: The benefit of anal flap advancement is that it is safe, avoids the risk of sphincter injury and has high healing rates. Therefore, it can be recommended as a safe viable alternative in the surgical treatment of chronic anal fissures.

General

Poster 027

Perfix plug hernioplasty improves the rate of daycase procedures

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Aims: Literature suggests that the plug hernioplasty compares favourably with the Lichtenstein repair, having particularly short and painfree recovery periods. The aim of this study was to analyse how the introduction of the plug technique affected the clinical practice of a single surgeon.

Methods: Plug hernioplasty replaced the Lichtenstein technique at the start of 1997, so we audited the 4-year period 31 March 1995 to 26 March 1999. The theatre register identified patients undergoing inguinal hernia repair, and case notes provided the relevant data on methods of anaesthesia, operation time and inpatient status.

Results: Some 346 patients underwent a total of 360 inguinal hernia repairs (116 Lichtenstein *versus* 244 plug repairs) of which 295 were performed for primary unilateral, 28 for bilateral and 37 for recurrent herniae. The table describes operation data for each year.

Year	Operations	General anaesthesia (%)	Local anaesthesia (%)	Mean op time (min) (range)	Daycases (%)	Inpatients (%)
1995	36	34 (94)	2 (6)	40 (20–70)	7 (19)	29 (81)
1996	62	60 (97)	2 (3)	42 (20–100)	11 (18)	51 (82)
1997	89	65 (73)	24 (27)	35 (18–56)	37 (42)	52 (58)
1998	142	107 (75)	35 (25)	30 (10–70)	93 (66)	49 (34)
1999	31	21 (68)	10 (32)	34 (15–90)	23 (74)	8 (26)

Throughout 1996, when the Lichtenstein technique was employed, 3 per cent of operations were performed under local anaesthetic (LA). In 1998, however, when plug hernioplasty was the repair of choice, 25 per cent were performed under LA, representing a significant increase, $P=0·0003$ (χ^2 test). Of the 116 Lichtenstein procedures performed, 22 (19 per cent) were daycases and 94 (81 per cent) were inpatients. Some 149 (61 per cent) of the patients undergoing plug hernioplasty were discharged the same day, and only 95 (39 per cent) required admission. The increase in the proportion of daycases since adopting the plug technique is significant, $P<0·0001$ (χ^2 test).

Conclusions: The introduction of the plug technique into a single surgeon's practice has reduced the number of patients requiring general anaesthesia, and significantly increased the number of operations performed as daycases.

Poster 028

Splenectomy and infection prophylaxis: wide variations in practice

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Aims: To study infection prophylaxis in adults undergoing elective and emergency splenectomy.
Methods: A retrospective case-note analysis was performed on 116 consecutive patients over a 5-year period at two large hospitals Indications for splenectomy and schedule of immunological and antibiotic prophylaxis were noted
Results: There were 61 emergency and 55 elective splenectomies. The median (range) age was 56 years (8–91) and the male·female ratio was 72·44. Perioperative prophylaxis patterns are summarized in the table.

	Elective (%)		Emergency (%)		Total (%)	
	Yes	No	Yes	No	Yes	No
Pneumococcal vaccine	100	–	80	20	90	10
HIB vaccine	75	25	69	31	72	28
Meningococcal vaccine	36	64	34	66	35	65
Postoperative antibiotics	87	13	87	13	87	13

Elective patients were vaccinated at a median 13·5 days preoperatively (IQR, 1–40), while emergency patients were vaccinated at a median 3 days postoperatively (IQR, 1–8)
Conclusions: There is a wide variation in the selection and timing of vaccines for perisplenectomy infection prophylaxis.

Poster 029

Suspected appendicitis in females of child-bearing age: the value of laparoscopy

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Aims: To assess the value of diagnostic laparoscopy in females of child-bearing age (14–40 years) with clinical diagnosis of acute appendicitis.
Methods: Between 1 January 1995 and 31 December 1996, 163 females aged 15–40 years who underwent diagnostic laparoscopy for suspected appendicitis were identified through a prospective database
Results: An abnormal appendix was identified in 71 patients (43·5 per cent), 56 had alternative pathology (33·4 per cent) and laparoscopy was normal in 36 (22·1 per cent). The negative appendicectomy rate was 9·8 per cent and the rate of gangrenous and perforated appendicitis 12·9 per cent In 52·2 per cent of patients, further surgical procedure was undertaken In 78 patients (47·8 per cent), no further surgical intervention was needed.
Conclusions: Diagnostic laparoscopy reduces both the negative appendicectomy rate and the rate of gangrenous and perforated appendicitis in women of child-bearing age

Poster 030

The cost of a specialist nutrition nurse is offset by savings produced by significantly reducing the rate of line sepsis

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Aims: Catheter-related sepsis remains the most common complication in patients receiving total parenteral nutrition (TPN). We prospectively assessed the impact of the introduction of a nutrition team on the incidence of TPN catheter-related sepsis and the cost of providing such a service
Methods: TPN was administered via a tunnelled Hickman line inserted under general or local anaesthesia using a uniform protocol. Patients were assessed daily for features of line sepsis. The cost of a nurse specialist and the cost of septic complications were calculated over each year according to hospital data.
Results: The results are summarized in the table.

	Year 1 ($n=56$)	Year 2 ($n=54$)	Year 3 ($n=49$)	Year 4 ($n=34$)	Year 5 ($n=35$)
Definite sepsis	28 (52)	2 (3·7)	1 (2)	1 (2·9)	1 (2·9)
Possible sepsis	N/A	3 (5·5)	2 (4)	0	0
Probable sepsis	N/A	5 (9·2)	2 (4)	0	0
Total sepsis	28 (52)	10 (18·4)	5 (10)	1 (2·9)	1 (2·9)
Cost of TPN and catheter replacement	£10293·36	£3676·20	£1138·10	£367·62	£367·62
Amount saved by CNS	N/A	£6249·54	£7868·59	£5881·92	£6065·73
Cost of nutrition service	N/A	£17500·00	£17500·00	£17500·00	£17500·00
Deficit	£10293·36	£11250·46	£9631·41	£11618·08	£11434·27

Percentages in parentheses Year 1 applies to the 12 months prior to employment of CNS

Catheter-related sepsis was significantly reduced following employment of a CNS ($P<0·01$).
Conclusions: The cost of the CNS salary is consistently offset by savings produced by a significant reduction in the rate of line sepsis

Poster 031

Successful management of chronic pain after inguinal herniorrhaphy

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Aims: To investigate the management and outcome of patients with chronic pain after inguinal herniorrhaphy
Methods: All patients referred to the chronic pain service in Leicestershire over a 10-year period were reviewed retrospectively.
Results: A total of 66 patients were identified, of whom data were complete on 60. There were 56 men, age range 17–79 years. Forty-nine herniae were primary repairs and 11 were recurrent Treatment modalities included wound infiltration with local anaesthetic 23, nerve blocks 18, transcutaneous nerve stimulator 6 and tricyclic antidepressants 6 cases. After treatment, 10 patients were cured, 33 were better, four were the same and five reported being worse than at first referral
Conclusions: Postherniorrhaphy pain is a small but significant problem which can be successfully managed in up to 75 per cent of cases by the techniques available to a chronic pain service.

Poster 032

Varicose vein surgery: the patients' early experiences after leaving hospital

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Aims: Following routine surgery, only limited data are available concerning the range of problems experienced by patients in the community, how they are managed, by whom, and their effects on everyday patient activity These matters were studied by means of a prospective multifactorial audit of varicose vein surgery.

Methods: Some 313 consecutive patients (male $n=99$, group median age, 46 years, range, 17–81) undergoing any form of varicose vein surgery in one health district were recruited. Follow-up was by a standardized telephone interview 2 weeks after surgery conducted by one researcher, and by a questionnaire 10 weeks later.
Results: The response rate at 2 weeks was 98 per cent and at 10 weeks was 76 per cent. During the first 2 weeks, reported morbidity included bleeding $n=37$ (12 per cent), ankle paraesthesiae/pain $n=27$ (9 per cent), phlebitis $n=23$ (8%), thigh pain $n=18$ (6 per cent), infection $n=17$ (6 per cent) and groin serous leak $n=12$ (4 per cent). Overall, 61 patients (20 per cent) were prevented from returning to work or normal activity by one of these problems. The use of skin clips for wound closure was associated with problems in 35/151 patients (27 per cent). Twenty-eight per cent consulted their GP on one occasion (more than once, 7 per cent). District nurse/practice nurse 23 per cent (more than once, 17 per cent) and 3 per cent attended the accident and emergency department. Ten per cent experienced complications related to discharge analgesia. Of those working ($n=205$), 31 per cent had returned to work by 2 weeks, 89 per cent by 1 month, 93 per cent by 2 months and all but one by 3 months. At 3 months, 53/239 (22 per cent) had developed new problems. These included cosmetic deterioration, aching, tender scars and leg swelling. Three per cent continued to experience troublesome pain or paraesthesiae. Overall, 22 per cent felt that the information they received on discharge was inadequate and 8 per cent were confused by advice from different sources.
Conclusions: In this study, varicose vein surgery was associated with appreciable morbidity after leaving hospital, which placed a burden on community-based healthcare services. Data such as this are not routinely available to the surgical team.

Poster 033

Audit of the outcome of emergency surgery in nonagenarians

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Aims: Advances socially and medically have increased the life expectancy of both men and women, and this continues to increase. With the elderly population expanding, the cost of care has increased out of proportion. In many studies, the age of the patient has influenced the outcome of surgery. However, when compared with other factors, age alone is not such a powerful predictor of outcome.
Methods: Over the period April 1996 to December 1998, 152 patients (124 females) over the age of 90 years were admitted as surgical emergencies. These patients constituted 176 admissions. Mean age was 92·3 years. Seventy-eight per cent of patients were admitted as a single admission. The diagnoses were divided as follows: lower GI, 53 per cent; upper GI, 15 per cent, vascular, 14 per cent; other, 18 per cent.
Results: Sixty-nine operations were performed, with a 30-day mortality of 25 per cent. Eighteen patients were admitted to the Intensive Care Unit, thirteen of which were discharged to the ward, and nine of these were finally discharged home. Seventy-two per cent of patients returned to their original homes or carers after discharge. However, by December 1998 45 per cent of patients had died from other causes.
Conclusions: An increasing population over the age of 90 years is increasing the demand on the healthcare system. However, we have shown that the majority present as acute admissions and are managed with low mortality. Therefore, chronological age should not be used as the only predictor of outcome and, when considering the very elderly, we must shift the emphasis on length of survival to maximizing quality of life.

Poster 034

Percutaneous varicocele embolization

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Aims: The aim of this study was to evaluate our early results of percutaneous varicocele embolization in a district general hospital.
Methods: We present a retrospective review of spermatic vein (SV) embolization using stainless steel occluding spring coils, to treat left-sided varicoceles.
Results: Between August 1994 and March 1999, embolization was attempted in 50 males, with median age 32 (range, 14–68) years. The commonest indication for intervention was pain in 45 (90 per cent), with four (8 per cent) for infertility and one (2 per cent) for swelling. Embolization was successfully performed in 35 (70 per cent) patients. Primary failure was associated with anomalous venous anatomy in 13 (26 per cent) patients, spasm prevented catheterization of the SV in one (2 per cent) patient and, in one (2 per cent) other, there was no demonstrable SV incompetence. The only complication noted was a small groin haematoma, which developed in a patient on aspirin. At follow-up (range, 2–52 weeks), clinical success, as determined by resolution of varicocele and symptoms or an increase in sperm count, was observed in 31 (89 per cent) patients in whom embolization was feasible. Of the two successful procedures performed for infertility, there has been one positive pregnancy to date. Three patients had the procedure repeated, one for technical failure (spasm), which was again unsuccessful, and two others for recurrence, one successful, the other failed to demonstrate any incompetence. Surgical ligation has subsequently been performed in eight (16 per cent) men in whom embolization was not accomplished.
Conclusions: Embolization allows precise occlusion of the SV and should be the first line of treatment for symptomatic varicocele. It is a minimally invasive procedure which is associated with low morbidity, and allows most patients to return to normal daily activity immediately.

Poster 035

Inguinal hernia repair in the new millennium: the surgeon's view

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Aims: The published literature is divided as to whether laparoscopic hernia repair is superior to open techniques, and laparoscopic hernia repair has not been accepted in the same way as has laparoscopic cholecystectomy. This survey was conducted to determine current practice in hernia repair, current attitudes to laparoscopic hernia repair and current opinion as to its likely role in the future.
Methods: A postal questionnaire was sent in August 1999 to 500 surgeons chosen randomly from a comprehensive list of practitioners of general surgery or one of the subspecialities thereof. The questionnaire required simply circling the responses to seven questions, although adequate provision for free text was made.
Results: Some 374 (74·8 per cent) surgeons responded. Thirty-four surgeons who had either retired or were no longer repairing hernias were excluded, leaving 340 replies for analysis. Only 18 respondents had no subspeciality interest. Open mesh repair was the technique of choice in primary unilateral hernia repair for 76·8 per cent of respondents, while 5·6 per cent preferred the shouldice repair, 5 per cent laparoscopic repair, with other techniques being rendered virtually obsolete. Half of all respondents have provided a laparoscopic hernia repair service, but 50 per cent of these have subsequently ceased to do so. The primary reasons for stopping were cost (32·3 per cent), complications (32·2 per cent) and a lack of benefit (20·7 per cent). Among surgeons currently performing laparoscopic repair, the favoured technique was the transabdominal preperitoneal approach (48·3 per cent). When asked about the future of hernia repair, only 7·6 per cent of all respondents thought it likely or very likely that the laparoscopic technique would become the method of choice; indeed, only 17·2 per cent of those actually using the technique thought it likely or very likely. Furthermore, 39·1 per cent of current practitioners would cease repairing hernias if laparoscopic repair becomes the accepted technique. Upper GI surgeons were most likely to continue (73·8 per cent), with vascular surgeons being least likely (48·8 per cent). If laparoscopic repair were to be the accepted operation, then the increased cost to the NHS annually would be in excess of £30 million.
Conclusions: Open, tension-free mesh repair is now overwhelmingly the technique of choice for the majority of surgeons practising inguinal hernia

repair, despite the conflicting data as to its superiority over laparoscopic repair. Future acceptance of laparoscopic as the technique of choice would have significant consequences for the provision of hernia services with respect to the numbers of available surgeons, the financial burden and the training of future surgeons; most likely to militate against the acceptance of laparoscopic repair, however, is the fact that most surgeons do not think it will become accepted.

Poster 036

The surgical registrars: learning agreements, the RITA and structured training

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Aims: Calmanization requires structured, individualized training based on written learning agreements and assessment of that training by the RITA (Record of In-Training Assessment). This study aimed to establish whether year 2 and 5 registrars in general surgery have learning agreements and if they regard the RITA as a fair assessment of their training.
Methods: After liaison with the JCHST (Joint Committee on Higher Surgical Training), the college provided the address list for all UK year 2 and 5 registrars in general surgery. A postal survey with selected follow-up telephone interview was performed. In the second part of the survey, trainees were required to identify who should be responsible for planning their annual rotation and weekly training structure.
Results: Some 98 SpR 5 and 49 SpR 2 registrars were surveyed. The response rates were 50 SpR 5 (53 per cent) and 21 SpR 2 (45 per cent). Thirteen per cent of respondents (15 per cent SpR 5, 6 per cent SpR 2, NS) had a written learning agreement. Seventy-five per cent (76 per cent SpR 5, 73 per cent SpR 2, NS) were in posts that met their training requirements and 60 per cent (61 per cent SpR 5, 56 per cent SpR 2, NS) received sufficient feedback. The provision of sufficient feedback was highly correlated with the meeting of training requirements (ϕ 0·49, $P < 0{\cdot}00001$). The RITA was considered 'an adequate assessment' by 30 per cent (25 per cent SpR 5, 43 per cent SpR 2, NS) and 35 per cent (34 per cent SpR 5, 37 per cent SpR 2, NS) considered it 'an honest dialogue'. Data collected on responsibility for rotation planning showed that trainees felt they should have the same level of influence as the RITA committee when it came to annual post allocation. In the planning of weekly training structure, the trainees felt that they should be able to negotiate this with their consultant on equal terms.
Conclusions: Training agreements are underutilized and the RITA process is poorly perceived. The majority are satisfied with their training but they feel a need to have greater influence over its planning.

Poster 037

Abstract withdrawn

Poster 038

Laparoscopic simulation: does performance improve with increasing surgical experience?

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Aims: If simulators are valid measures of actual laparoscopic skill, then simulator performance should improve with increased levels of surgical experience. The aim of this study was to compare laparoscopic simulator performance of basic surgical trainees with that of laparoscopically naive and expert groups.
Methods: Thirty-six basic surgical trainees, 37 medical students and 15 consultant general surgeons were studied. All subjects performed two tasks on both conventional box (Ethiskills, UK) and virtual reality (MIST-VR; Ethiskills, UK) laparoscopic trainers under standardized environmental conditions and after identical instruction. Error rate, economy of movement (MIST-VR only) and time taken to complete tasks on each simulator were recorded. The performances of the three groups were then compared using the Kruskal–Wallis test.
Results: There was a significant difference between the three groups in the time taken to complete the tasks on the conventional box trainer. Consultants were faster than both trainees ($P < 0{\cdot}001$, Mann–Whitney) and students ($P < 0{\cdot}001$, Mann–Whitney), trainees, however, were not significantly faster than students ($P = 0{\cdot}07$, Mann–Whitney). No significant difference was found between the groups in error score on the conventional box trainer or time, error or economy score on MIST-VR.

	Conventional (median (IQR))		MIST-VR (median (IQR))		
Group	Time (s)	Error	Time (s)	Error	Economy
Student	614 (553–769)	13 (7–18)	248 (205–309)	9·6 (6·7–13·8)	25·1 (1·1–28·8)
SHO	564 (512–671)	10·5 (7–18)	223 (188–292)	8·5 (6·5–12·0)	25·9 (18·9–31·9)
Consultant	371 (334–447)	11 (6–17)	231 (195–270)	8·6 (8·0–11·1)	21·0 (18·4–23·4)
P (Kruskal–Wallis)	<0·0001	0·812	0·390	0·167	0·621

Conclusions: Increasing surgical experience reduces time taken to complete tasks on a conventional box trainer but does not appear to lead to improved performance on the virtual reality simulator. Further work is needed before MIST-VR is introduced for formal laparoscopic skill assessment.

Poster 039

Impact of intermittent sequential pneumatic compression (ISPC) devices on adverse cardiovascular influence of positive-pressure pneumoperitoneum

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Aims: To study the influence of a new ISPC (Lymphapress) on the adverse cardiovascular effects of positive-pressure pneumoperitoneum (PPPn) in laparoscopic surgery.
Methods: Lymphapress is a new thigh-length ISPC legging. The system was used in 10 consecutive patients (American Society of Anesthesiology (ASA) I/II) undergoing laparoscopic cholecystectomy at PPPn of 12 mmHg and 30° head-up tilt. Cardiac output (CO; L min^{-1}), stroke volume (SV; mL), blood pressure (BP) and pulse rate were measured at 3-min intervals by transoesophageal Doppler at the following: (1) pre-PPPn in supine position under general anaesthesia, (2) PPPn and head-up tilt with Lymphapress off; (3) PPPn and head-up tilt with Lymphapress on; (4) post-PPPn in supine position under general anaesthesia. The Wilcoxon rank signed test was used for the nonparametric data, which are presented as median percentage change (IQR).
Results: PPPn and head-up tilt resulted in reductions in CO by 20 per cent (4, 37) ($P = 0{\cdot}037$) and in SV by 18 per cent (8, 23) ($P = 0{\cdot}022$) without any significant change noted in BP or pulse rate ($P = 0{\cdot}878$). Activation of Lymphapress during PPPn and head-up tilt resulted in rises in CO by 27 per cent (17, 31) ($P = 0{\cdot}007$) and in SV by 16 per cent (10, 34) ($P = 0{\cdot}007$). There was no significant difference observed in any of the parameters between pre-PPPn in the supine position (stage 1), and during PPPn and head-up tilt with Lymphapress activated (stage 3) ($P > 0{\cdot}1$). All parameters were restored following abdominal desufflation ($P > 0{\cdot}1$).
Conclusions: The Lymphapress reverse the adverse cardiovascular effects of PPPn and head-up tilt during laparoscopic surgery.

Poster 040

Changes in haematological and biochemical parameters after pancreas resection combined with purified or unpurified islet autotransplantation

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Aims: Intraportal islet autotransplantation (IAT) can lead to portal hypertension and pathological changes in liver function. This study assessed haematological and biochemical changes after either purified or unpurified intraportal IAT.
Methods: Eighteen patients (12 female, six male) underwent pancreas resection with either unpurified or purified intraportal IAT. Islets were purified on a Ficoll-based gradient on a COBE processor. Purity ranged from 40 to 90 per cent. Mean arterial pressure (MAP) and portal pressure were measured during islet infusion.
Results: Islet count per gramme of pancreas were similar in both groups (2092 *versus* 2072 IEQ g^{-1}). The mean volume of islet tissue was also similar (10·6 *versus* 9·9 mL). Significant pathological increases in portal pressure, APPT and ALT occurred in both groups after IAT.

	Purified ($n=11$)		Unpurified ($n=7$)	
	Preinfusion	Postinfusion	Preinfusion	Postinfusion
MAP (mmHg)	87·3	75·0*	90·4	74·5*
Rise portal *P* (mmHg)		7·6		7·0
Platelets (*n* 150–400 × 10^9 L^{-1})	249	128*	285	163*
APPT (*n* 1·0)	1·0	1·4*	1·0	3·4*
INR (*n* 1·0)	1·0	1·6*	1·0	1·7*
ALT (*n* 2–53 IU L^{-1})	27	169*	22	214*
ALP (*n* 40–130 IU L^{-1})	69	108	62	118
Bilirubin (*n* 3–17 µmol L^{-1})	9	21	11	13

All mean values $*P<0·05$ (Wilcoxon)

Conclusions: Intraportal IAT leads to transient pathological changes in haematological and biochemical parameters but these are not ameliorated by islet purification.

Poster 041

The value of preoperative laparoscopic assessment in suspected ampullary cancer

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Aims: To determine the usefulness of laparoscopic assessment of suspected ampullary neoplasms, prior to exploratory laparotomy.
Methods: Between January 1990 and August 1999, 85 patients suspected of having an ampullary neoplasm were evaluated and 63 were considered fit for surgery with no obvious signs of irresectability (based on results of CT scanning and ERCP). Two groups of patients were identified – those who proceeded directly to resection and those who underwent laparoscopic evaluation prior to attempted resection (after 1993). Information gathered from laparoscopy included presence of metastasis, local resectability as judged by laparoscopic ultrasonography and tumour size.
Results: Of 39 patients undergoing laparoscopic evaluation, five patients (13 per cent) were found to have either metastasis or portal vein involvement and were referred for palliative ERCP and stent placement; five patients (15 per cent) who underwent laparotomy were found at surgery to be unresectable, despite laparoscopic evaluation and underwent palliative biliary and gastric bypass. Of 24 patients proceeding directly to laparotomy, 22 were resected – two had liver metastasis and underwent operative bypass. Six of the original group of 85 patients underwent late laparotomy for either biliary or duodenal obstruction. Two of these patients had undergone previous laparoscopic evaluation.
Conclusions: Laparoscopic evaluation of suspected ampullary neoplasms prevented unnecessary laparotomy in only 13 per cent of patients, and 92 per cent of patients who proceeded directly to surgery underwent successful resection. Additionally, the incidence of late laparotomy in unoperated patients who went on to either duodenal or biliary obstruction may support operative intervention in most suspected case of ampullary neoplasm.

Poster 042

Outcome of endoscopic treatment of acute postinflammatory pancreatic pseudocysts

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Aims: Recent evidence attests to the safety of the endoscopic approach for the treatment of pseudocysts complicating chronic pancreatitis and, on this basis, these techniques are increasingly attempted for the treatment of pseudocysts complicating acute pancreatitis. The aim of this study is to evaluate the outcome of endoscopic treatment for acute postinflammatory pancreatic pseudocysts.
Methods: Patients with a diagnosis of pancreatic pseudocysts were identified from the Lothian surgical audit database for the 4-year period March 1995 to March 1999. Acute postinflammatory pseudocysts were defined in keeping with Atlanta consensus conference criteria (index presentation with abdominal pain and hyperamylasaemia with computed tomographic or ultrasound evidence of pancreatic inflammation but without pseudocyst on initial imaging). Other pseudocysts were classified as chronic (initial presentation with pseudocyst, no obligatory history of abdominal pain). Using these criteria, 14 of 21 pseudocysts were classified as acute and seven as chronic. Median delay from index admission to pseudocyst intervention in the acute group was 8 (6–16) weeks.
Results: Endoscopic transgastric cystgastrotomy using the side-viewing duodenoscope combined with insertion of a pigtail endoscopic stent was successful in 3/14 (21 per cent) of acute postinflammatory pseudocysts and three of seven chronic pseudocysts (43 per cent) (P=NS, Mann–Whitney *U* test). In the acute group, endoscopic therapy was complicated by haemorrhage requiring urgent surgery in three (21 per cent) and by failure to clear a debris-laden pseudocyst cavity in 11 (79 per cent). Surgical treatment for endoscopic treatment failure resulted in successful resolution of the pseudocyst in 11 (79 per cent) acute patients. There were no deaths in this group, either after endoscopic therapy or after surgical treatment.
Conclusions: The numbers in this study are small but tend to support the use of endoscopic therapy for chronic pancreatic pseudocysts but not for acute postinflammatory pseudocysts with debris-laden cavities. Our data underline that a randomized comparison of endoscopic with surgical treatment of postinflammatory pseudocysts remains ethically appropriate and practical, and would provide the optimum answer to acute pseudocyst management.

Poster 043

Developing a prognostic index for patients with colorectal hepatic metastases

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Aims: Analyses to identify independent determinants of outcome in patients with hepatic metastases from colorectal cancer are usually based on groups already defined by treatment The aim of this study is to derive a prognostic index based on a relatively unselected group of patients, with a view to aiding clinical decision-making

Methods: Data were collected prospectively on 245 patients referred between 1989 and 1998 to a specialist hepatobiliary unit for consideration of resection of metastases. Preoperative risk factors relating to primary tumour, metastatic disease and patient characteristics were the bases of univariate and multivariate analyses using the Cox proportional hazards method

Results: A prognostic index was derived based on the number of metastases (less than 3, 4 or more) and preoperative albumin, alkaline phosphatase and CEA Three outcome groups were identified comprising the lowest and highest quartile and the middle 50 per cent. Comparison of survival curves using the Kaplan–Meier method showed significant differences in median survival between the three categories category 1, 48 months (14–81); category 2, 23 months (16–29); category 3, 10 months (8–13), $P<0\cdot00001$ (log rank=49·4). Two other scoring systems (as reported by Iwatsuki in 1999, and the Memorial Sloan Kettering Cancer Center reported by Y. Fong in 1999) were applied to these data, neither allowing clear discrimination between all the groups

Conclusions: A useful prognostic index must be generalizable to independently collected data, and an individual institution may not generate a large enough data set to ensure reliable results. These problems would be addressed by the establishment of a national liver resection database on which to base further research in this area.

Poster 044

Management of polypoid lesions of the gallbladder

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Aims: As ultrasound technology has improved, an increasing number of polypoid lesions of the gallbladder (PLG) are being detected We aim to review a district general hospital's experience of these lesions and discuss their controversial management.

Methods: Thirty-eight patients with ultrasonically detected PLG were reviewed with their demography, radiology and pathology defined.

Results: Thirty-four underwent cholecystectomy (four were advised against or declined operation), of which 11 (32·4 per cent) had macroscopic and histopathologically proven PLG: seven (20·6 per cent) had cholesterol polyps, two (5·9 per cent) had adenomas, one had a carcinoid tumour and one had an adenocarcinoma of the gallbladder. One patient undergoing cholecystectomy had a histopathologically normal gallbladder and the remainder had chronic cholecystitis with or without gallstones.

Conclusions: We propose a protocol for the management of ultrasonically detected PLGs In this protocol, we suggest that patients with a PLG should undergo surgery if they are symptomatic, or if the PLG is 1·0 cm or more in diameter

Poster 045

Training experience of higher surgical trainees in staging laparoscopy/laparoscopic USS for HPB malignancy

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Aims: Laparoscopic staging has become a valuable investigative tool in the assessment of patients with hepatopancreatobiliary (HPB) malignancy. Defining the learning curve for surgical trainees has not previously been described.

Methods: Between January 1999 and October 1999, 58 patients underwent staging laparoscopy for HPB malignancy Higher surgical trainees with no previous experience undertook initial assessment and recorded their findings. Assessment was subsequently performed by an experienced consultant and findings compared

Results: Four trainees undertook a median of 13 procedures (range, 9–24). The provisional diagnosis was secondary liver tumour (10), primary liver tumour (seven), benign liver lesion (two), cholangiocarcinoma (eight), pancreatic tumour (31). Trainees identified 93 per cent of abnormal findings seen at laparoscopy. Consultants completely agreed with findings of trainees in 23 of 25 patients (92 per cent) assessed by laparoscopic ultrasonography for hepatic pathology. Identified of vascular structures around the pancreas by laparoscopic ultrasonography (LapUS) was misinterpreted by trainees in 16 per cent of cases Trainees failed to identify a tumour mass in five of 24 cases (21 per cent), portal vein involvement in seven of 13 cases (54 per cent) and lymphadenopathy in five of 10 cases (50 per cent). Overall, trainees incorrectly assessed resectability of pancreatic tumours in three of 33 cases (9 per cent).

Conclusions: Higher surgical trainees with no previous experience in laparoscopic staging performed very well at screening laparoscopy for HPB malignancy and LapUS of hepatic pathology, suggesting these techniques can be learnt rapidly. However, LapUS assessment of pancreatic pathology was significantly more difficult, implying that the learning curve for this technique is considerably longer.

Poster 046

Operative mortality after pancreatoduodenectomy

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Aims: Perioperative mortality limits the extension of pancreatic surgery to the older and less-fit patient. The aim of this review was to determine the cause and identify factors which will prevent these deaths

Methods: Data on all patients undergoing pancreatoduodenectomy between May 1976 and October 1999 were collected prospectively and analysed retrospectively A total of 514 procedures were performed: 15 patient had undergone a primary total pancreatoduodenectomy and 11 had had a prior distal pancreatectomy, leaving 488 for analysis Patients were subdivided into five groups: I, 1–100; II, 101–200, III, 201–300; IV, 301–400; V, 401–488. The median age was 51 (13–84) years and 388 (63·3 per cent) were male Resection was undertaken for malignancy in 270 (55·3 per cent), benign neoplasms in 29 (5·9 per cent), benign inflammatory disease in 186 (38·1 per cent) and haemorrhage in three patients. The resection was elective in 474 (97·1 per cent) and pylorus preserving in 278 (57·0 per cent).

Results: Death occurred in 22 patients – 5·9 per cent of those with malignant disease and 2·8 per cent of those with benign disease. Urgent resection had a higher mortality (14·3 per cent). Mortality decreased over time group I, 7 per cent; II, 5 per cent; III, 5 per cent; IV, 4 per cent; V, 1·1 per cent. The deaths occurred in hospital (20) or within 60 days of surgery at home (two) at a median of 21 days (range, 1–100). In the first postoperative week, there were four deaths, three in week 2, four in week 3, four in week 4, and the remainder (seven) occurred later. Four deaths were due to primary extra-abdominal disease: pulmonary embolus (two), myocardial infarct (one) and pneumonia with renal failure (one). Intra-abdominal causes were multifactorial with haemorrhage (10), enteric leak (one), pancreatic fistula (one), pancreatitis (two), small bowel ischaemia (one) and sepsis (three) being the dominant cause Sepsis underlay many of the deaths caused by bleeding and respiratory problems. The grumbling pyrexia was a harbinger of problems.

Conclusions: Further reduction in mortality will be achieved by aggressive investigation and management of sepsis and haemorrhage

Poster 047

Laparoscopy and laparoscopic ultrasonography in the staging of pancreatic cancer in a tertiary referral unit

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Aims: To determine the use of laparoscopy and laparoscopic ultrasonography (lapUS) in addition to CT scanning in the staging of pancreatic pathology in a tertiary referral unit.
Methods: A retrospective analysis of 108 patients with a potentially resectable pancreatic cancer diagnosed between October 1996 and September 1999 were reviewed Data collected included TNM staging and assessment of resectability with regard to CT, laparoscopy and lapUS, surgery and pathology.
Results: Of the 108 patients, 78 (72 per cent) had a surgically resectable pancreatic disease Of these 78 resected cases, 39 had PDAC (74 per cent of these were node positive), 21 (27 per cent) had ampullary adenocarcinoma (43 per cent of these were node positive), six patients (8 per cent) had chronic pancreatitis and 12 (15 per cent) had other pathology. Assessment of resectability by CT showed a sensitivity of 96 per cent and a specificity of 40 per cent. There were 18 false positives (nine liver metastases, four locally advanced tumours, three vascular invasions and two peritoneal metastases were missed) and three false-negatives (two metastases and one vascular invasion were diagnosed incorrectly) Assessment of resectability by laparoscopy alone showed a sensitivity of 99 per cent and a specificity of 70 per cent. Laparoscopy with lapUS showed a sensitivity of 97 per cent and a specificity of 77 per cent Increased specificity by lapUS was owing to the detection of additional liver metastases and a locally advanced tumour missed by laparoscopy alone
Conclusions: CT scanning is useful for the initial diagnosis and staging of pancreatic cancer but is inaccurate at detecting metastatic disease Laparoscopy with the addition of lapUS adds to the staging process.

Poster 048

Randomized placebo-controlled double-blind trial of ropivacaine in laparoscopic cholecystectomy

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Aims: The value of local anaesthetics to reduce postoperative pain after laparoscopic cholecystectomy is unclear. The long-acting local anaesthetic ropivacaine has a substantially higher maximum dose than bupivacaine; its value at maximum dose was assessed
Methods: In a randomized trial, 80 patients undergoing laparoscopic cholecystectomy, with standardized anaesthesia and diclofenac 100 mg PR at induction, were given 100 mL of ropivacaine (2 mg mL^{-1}) or normal saline into the subcutaneous, muscle and subperitoneal layer of the port sites (50 mL), the gall bladder bed (20 mL) and under the right diaphragm (25 mL) Postoperative analgesia was with oral co-codamol and diclofenac with IM morphine for rescue analgesia Values are medians and interquartile ranges (Mann–Whitney *U* test).
Results: In each group, only 17 required postoperative morphine (χ^2 = 0 01, 1 d f , *P* = 0·92).

Hours postop	Linear analogue pain score			Peak expiratory flow rate % of preop		
	Ropivacaine	Placebo	*P* value	Ropivacaine	Placebo	*P* value
1	17 (0–42)	25 (3–44)	0 56	60 (46–75)	60 (44–69)	0 83
4	23 (7–42)	21 (10–34)	0 63	70 (53–85)	69 (48–81)	0 52
6	20 (6–42)	20 (4–30)	0 32	77 (57–88)	76 (50–89)	0 56
24	16 (5–30)	12 (3–29)	0 32	85 (71–96)	75 (57–91)	0 13

Conclusions: Local anaesthetics do not have a clinically significant effect on postoperative pain or analgesic requirement after laparoscopic cholecystectomy.

Poster 049

Pancreaticoduodenectomy for cancer complications, recurrence and survival

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Aims: To analyse results of pancreaticoduodenectomy for cancer as regards postoperative complications, tumour recurrence and survival.
Methods: A retrospective analysis was performed on patients who underwent a pancreaticoduodenectomy for cancer during the 5-year period 1991–95 Demographic data, preoperative drainage, laboratory data, postoperative complications, histopathological findings, time to recurrence, pattern of recurrence and survival time were documented on a database. A univariate and multivariate analysis using Cox regression model was undertaken to evaluate factors governing survival.
Results: Sixty-seven patients underwent pancreaticoduodenectomy for cancer during the study period (42 ampullary cancer, 17 pancreatic cancer, eight bile duct cancer). Preoperative drainage was undertaken in 52 (78 per cent) patients Major postoperative complications resulted in 16 (24 per cent) patients and were significantly higher in patients with low preoperative serum albumin (*P* = 0·01) The most common major complications encountered were pancreatic leakage (13 per cent), abdominal collections (5 per cent), and bleeding (2 per cent). Inpatient mortality was 3 per cent After a median of 29·8 months of follow-up, 38 (57 per cent) patients had developed tumour recurrence This was within the abdomen in 84 per cent, extra-abdominal in 11 per cent and widespread in 5 per cent Abdominal recurrence was diffuse in 37 per cent, local in 30 per cent, hepatic in 18 per cent and nodal in 15 per cent The 3-year actuarial survival rate for ampullary, pancreatic and bile-duct cancer were 58 per cent, 27 per cent and 25 per cent respectively. Univariate analysis revealed that tumour stage, tumour site, tumour differentiation, perineural invasion and lymphatic involvement were significant predictors of survival. Multivariate analysis showed that lymph-node involvement and tumour differentiation were the only two significant independent determinants of survival
Conclusions: Pancreaticoduodenectomy for cancer is associated with an acceptable morbidity and low mortality but is still associated with a high recurrence rate.

Paediatrics

Poster 050

The treatment of perianal abscess in children

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Aims: A high incidence of fistula *in ano* has been reported in children presenting with perianal abscess, and a search for a fistula and fistulotomy at the time of primary drainage had been advocated. By reviewing children presenting to our institution with perianal abscess, we determined the association between perianal abscess and fistula *in ano*, and propose a management plan for these conditions
Methods: Retrospective case-note review was performed over a 10-year period (January 1989 to January 1999), for all patients who had presented with a perianal abscess
Results: Sixty-nine patients were identified (63 males); age range, 1 month–12 years, mean, 4·3 years Of these, 65 (94 per cent) were

treated by incision and drainage alone. A fistulous tract was identified at primary drainage in five (7·2 per cent) of the patients. Eleven (15·9 per cent) had a recurrent abscess, seven (10·1 per cent) had a fistula *in ano* identified at follow-up and three (4·3 per cent) had both a recurrent abscess and fistula *in ano* The total incidence of fistula *in ano* was 21·4 per cent (15 patients)

Conclusions: Perianal abscess should be considered a rare condition in childhood, with the concomitant finding of a fistula *in ano* being close to 20 per cent, in contrast to other groups who report values of up to 75 per cent Searching for a fistula *in ano* at the time of primary drainage may create a tract and we advocate that perianal abscess should be treated by incision and drainage alone, and a fistula *in ano* treated as a second procedure.

Poster 051

Presentation and management of juvenile onset inflammatory bowel disease in the north-east of Scotland

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Aims: To audit the presentation and management of juvenile onset inflammatory bowel disease.

Methods: This was a retrospective study of all patients aged 16 years or under diagnosed with inflammatory bowel disease in one health region between 1980 and 1998. The patients were identified from computer-coding records and the following variables studied· age, sex, mode of presentation, medical and surgical management and length of follow-up.

Results: Eighty-five patients were identified, 60 with Crohn's disease and 25 with ulcerative colitis The incidence of ulcerative colitis and Crohn's disease has risen from 0·9 per 100 000 and 2·8 per 100 000, respectively, in the years 1980–89 to 1·6 per 100 000 and 4·1 per 100 000 in the period 1990–98 The majority of patients were diagnosed within 1 year of the onset of their symptoms, these were principally abdominal pain, diarrhoea and rectal bleeding. The mean age at presentation was 9·8 years for ulcerative colitis and 11·3 years for Crohn's disease The average length of follow-up was 7·1 years. Analysis of the surgical management of Crohn's patients has revealed a low rate of surgical intervention.

Conclusions: This study has demonstrated an increasing incidence of inflammatory bowel disease in the Grampian region of Scotland, coupled with a low rate of surgical intervention in Crohn's disease. These findings could be the result of early referral and diagnosis, with the disease being documented earlier in its course and/or more aggressive pre-emptive medical therapy.

Poster 052

Abdominoscrotal hydrocele in infancy: a surgical approach

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Aims: An abdominoscrotal hydrocele presenting in infancy is a rare but surgically difficult problem to deal with successfully Total excision of the hydrocele has previously been the recommended surgical treatment This study reports on the clinical features, investigation and anatomy of this condition, and recommends a staged groin and scrotal procedure as definitive management.

Methods: Eight children aged between 4 and 6 months presented with enormous hydroceles between 1996 and 1998. Ultrasonogrpahy confirmed the suspected presence of an abdominoscrotal hydrocele in all cases Two patients underwent a combined groin exploration and Jaboulay procedure, which we found technically difficult In the remaining six patients, the operation was staged On exploration of the groin, no patent processus vaginalis was found in any patient The hydrocele sac was found to pass through the deep ring and end blindly in the retroperitoneal space Excision of this abdominal component was easily achieved through the groin after aspiration of the fluid. Six to eight weeks later, a Jaboulay procedure was performed using a scrotal incision, so avoiding radical excision of the hydrocele sac

Results: One patient was noted to have a unilateral dysmorphic testicle One patient developed an infected scrotal haematoma that required drainage. Complete resolution of the hydroceles with a palpable testis was achieved in all patients.

Conclusions: An abdominoscrotal hydrocele in infancy is easily diagnosed by ultrasonography and may be treated by a staged groin exploration and Jaboulay procedure.

Poster 053

Umbilical and epigastric herniae in children – is surgical repair necessary?

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Aims: Most texts still recommend surgical repair of umbilical and epigastric herniae in children over the age of 3 years. To determine the correctness of this advice, we reviewed management and outcome of children with these herniae under the care of one consultant.

Methods: The case notes and management of all children seen with umbilical or epigastric hernia in the outpatient clinic from 1990 and 1994 were reviewed. Follow-up details were recorded either from hospital notes or by contacting the parents where possible

Results: Forty-three children presented with an umbilical hernia, of whom 14 were operated on (six of these because of pain), 15 closed spontaneously, three were persistent without symptoms and, in 11, no follow-up was available Ten children were seen with an epigastric hernia, of whom one was repaired because of pain, one closed spontaneously, six asymptomatic herniae persisted at the time of review and, in two cases, no follow-up was possible.

Conclusions: Most umbilical and epigastric herniae in children of all ages are asymptomatic and complications are rare. Most umbilical herniae close spontaneously, although some persist without symptoms, as do most epigastric herniae Therefore, surgery is rarely necessary, even in children over the age of 3 years.

Poster 054

Spontaneous resolution of pancreatic masses in children

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Aims: To review the clinical course and management of four children who presented recently to our centre with symptomatic pancreas masses.

Methods: We retrospectively reviewed the case notes, radiology and histology of these children who have presented over the past 3 years. We also reviewed the literature on idiopathic fibrosing pancreatitis and pancreatic masses in children

Results: Three children presented with obstructive jaundice, of whom all had abdominal pain and persistent vomiting was a feature of one. One child had abdominal pain alone. Three of the children had discrete masses in the pancreatic head, while the fourth had diffuse enlargement of the pancreatic head, neck and body None had a significantly raised serum amylase. Two children underwent pancreatic biopsy, with T-tube insertion

in one. Histology in these two cases showed a fibrotic, chronic inflammatory reaction consistent with idiopathic fibrosing pancreatitis – a rare childhood condition which has previously been treated by permanent biliary drainage, choloenteric bypass or sphincterotomy. No aetiological factor was identified Full resolution of presenting symptoms has been seen in all cases. Resolution of the radiological findings again occurred in all cases, with three to normal and one to a degree of atrophy.
Conclusions: (1) Obstructive jaundice secondary to idiopathic fibrosing pancreatitis may resolve spontaneously, avoiding the need for surgical intervention (2) Biopsy of a pancreatic mass in children may not always be necessary.

Transplantation

Poster 055

Side-effect profile of rapamycin in patients with chronic allograft nephropathy

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Aims: Rapamycin (Rapa) has been proposed as a possible treatment for chronic allograft nephropathy (CAN), with potential benefits over cyclosporin (CyA) dose reduction. However, it has potential haematological and hyperlipidaemic actions that may have significant implications for patients with poor renal function taking it for prolonged periods. This has not been investigated previously and the aim of this study was to characterize this in detail.
Methods: Thirty renal transplant recipients with biopsy-confirmed CAN taking CyA for immunosuppression with serum creatinines between 150 and 320 µmol L^{-1} were recruited. They were randomized to receive either a dose reduction in CyA that maintained trough levels at 50–75 ng L^{-1} (control), or a dose reduction in CyA with the addition of Rapa 2 mg day^{-1} Patients were followed up at 1, 2, 4, 6, 8, 12 and 24 weeks, and assessed for side effects, FBC, LFT, glucose, cholesterol, triglycerides, LDL and HDL and serum CMV status.
Results: Both groups were well matched in terms of patient characteristics, mean time after transplantation and original renal function Mean CyA trough levels after dose reduction were similar in both groups (Rapa 68 ± 21 *versus* control 56 ± 19 ng mL^{-1}; $P=0{\cdot}10$) and Rapa trough levels had stabilized by 4 weeks with a mean of 7.7 ± 3.4 ng mL^{-1}. Arthralgia (Raja 5/15 *versus* control 0/15, $P=0.04$) was reported more commonly but the incidence of headaches (Rapa 7/15 *versus* control 3/15, $P=0.25$), mild gastrointestinal upset (Rapa 5/15 *versus* control 1/15, $P=0.17$), infections and CMV antigenaemia were not significantly different Rapa was stopped in two patients: for a severe rash and for cholestatic jaundice.

	Control ($n=15$)		Rapamycin ($n=15$)	
	Pre	Post	Pre	Post
Hb (g dL^{-1})	12.1 (1.8)	12.2 (1.9)	12.4 (1.5)	11.2 (1.4)**
Glu (mmol L^{-1})	5.6 (1.5)	4.9 (1.2)*	4.6 (0.8)	4.7 (0.6)
Chol (mmol L^{-1})	5.6 (1.3)	5.3 (1.2)	5.5 (1.1)	5.7 (0.3)
TGs (mmol L^{-1})	1.8 (0.9)	1.9 (0.9)	1.6 (1.0)	2.4 (1.0)**

Values expressed as mean (s.d.) $^*P<0.05$, $^{**}P<0.025$ Paired two-tailed *t*-tests

Conclusions: Rapa has an acceptable side-effect profile and can be safely given to patients with CAN Anaemia and hypertriglyceridaemia occur after Rapa therapy but these effects are not dramatic at a dose of 2 mg day^{-1}.

Poster 056

Analysis of side effects after renal transplantation using either tacrolimus or Neoral immunosuppression – a prospective randomized trial

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Aims: After transplantation across an allogeneic barrier, there is a need for immunosuppression to prevent graft rejection; however, there are significant side effects. The aim of this study was to compare the profile of side effects in patients receiving either tacrolimus or Neoral immunosuppression after renal transplantation.
Methods: All patients over a 2-year period were randomized to receive either tacrolimus (0·2 mg kg^{-1}) or Neoral (15 mg kg^{-1}) immunosuppression combined with oral steroid. Recipients of an NHBD received a 50 per cent dose reduction. During the first 3 months, a reducing regimen of Neoral was used to maintain whole blood trough levels of 200–400 ng L^{-1}. Tacrolimus was reduced to maintain whole blood trough levels between 8 and 15 ng mL^{-1} To assess the onset of diabetes, all patients had a 75 g oral glucose tolerance test, along with HbAlc levels. Patients also completed questionnaires incorporating a 100-mm visual analogue scale (VAS) and a verbal response scale to assess other side effects.
Results: Overall, 68 patients were randomized to receive either Neoral or tacrolimus. The side-effect profiles are summarized in the table.

	Neoral	Tacrolimus
Diabetes		
3 month fasting glucose (mmol L^{-1})	4.7	6.0*
2 h glucose (>11 mmol L^{-1})	2 (9)	7 (30)
3 month HbAlc (%)	7.3	7.6
VAS		
Hirsutism	41.7	21.8*
Tremor	32.6	39.5*
Gum hyperplasia	13.7	6.5*
Diarrhoea	1.5	12.8
Abdominal pain	5.5	12.9

All mean values unless stated (percentages) $^*P<0.05$

Conclusions: Neoral and tacrolimus have different side-effect profiles but perhaps any advantage offered by tacrolimus is offset by the high incidence of glucose intolerance. Long-term follow-up is, therefore, required to assess the onset of diabetic complications in patients receiving tacrolimus immunosuppression.

Poster 057

Measurement of intrarenal resistance during pulsatile machine perfusion accurately predicts warm ischaemic injury

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Aims: Nonheartbeating donor (NHBD) kidneys are subjected to a variable degree of warm ischaemic injury and this has been associated with higher rates of graft dysfunction. Pulsatile machine perfusion (MP) systems may prove to be helpful in transplant tests of ischaemic injury situation. Therefore, the aim of this study was to determine the relationship between renal warm ischaemic injury and haemodynamic parameters during MP.
Methods: Kidneys ($n=36$) from 40 kg pigs were subjected to *in situ* warm ischaemic injury for periods of 10, 15, 30, 45, 60 and 90 min The kidneys were retrieved, flushed and then transferred back to the base hospital, where they were preserved by pulsatile machine perfusion for 6 h at a systolic pressure of 60 mmHg. Perfusate flow was measured and intrarenal resistance (IRR) was calculated as mean pressure/flow.

Results: IRR measured in the first 10 min of perfusion correlated well with warm ischaemic injury time (see table) MP over 6 h led to a reduction in IRR in all groups but the greatest falls in IRR were seen in kidneys with the longest warm times.

Warm ischaemic time (min)	Mean IRR over first 10 min ± s d ($mmHg\ mL^{-1}\ min^{-1}$)	Mean IRR over last 10 min ± s d ($mmHg\ mL^{-1}\ min^{-1}$)
10	1 36 (±0 13)	0 84 (±0 01)
15	2 40 (±0 18)	0 99 (±0 01)
30	2 78 (±0 19)	0 78 (±0 01)
45	3 91 (±0 17)	1 42 (±0 02)
60	4 29 (±0 17)	1 63 (±0 01)
90	5 91 (±0 67)	1 21 (±0 01)

Conclusions: Early measurement of IRR during pulsatile MP provides an accurate assessment of the duration of warm ischaemic injury This may prove to be of considerable clinical benefit as a pretransplant viability test which facilitates safe access to the NHBD pool and MP itself may be a way of minimizing the deleterious effects of warm ischaemia.

Poster 058

Relative effect of acute rejection on delayed graft function in recipients of asystolic or cadaveric donor kidneys

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Aims: The combined effects of acute rejection (AR) and delayed graft function (DGF) are detrimental to renal allograft graft survival The aim of this study was to assess the impact of acute rejection episodes in recipients of an asystolic or cadaveric (CAD) donor kidney with DGF.

Methods: All recipients of an NHBD kidney ($n = 69$) or cadaveric kidney ($n = 66$) with DGF were retrospectively identified over a 10-year period. Delayed graft function was defined as the need for dialysis within the first 7 days after transplantation, with the exception of those required for fluid overload and hyperkalaemia Primary immunosuppression comprised either cyclosporin or tacrolimus All patients with DGF underwent weekly needle core biopsies using ultrasound guidance to exclude AR. Histologically confirmed AR was graded according to severity and treated with intravenous steroid AR episodes resistant to steroid were treated with ATG. All patients with primary non-function were excluded from analysis.

Results: Of those patients receiving an NHBD kidney (22F:47M; median age, 49 years), 94 per cent experienced DGF Conversely, of those receiving a CAD kidney ($n = 440$), the incidence of DGF was 15 per cent Both groups were well-matched and the results are compared in the table

	AR	No AR	AR	No AR
Recipient age (years)	50	49	42	46
Donor age (years)	47	49	42	45
HLA–DR mismatch	13 (80)	26 (49)	13 (65)	17 (37)
Anastomosis time (min)	29	30	36	31
Cold ischaemic time (h)	16	17	22	16
DGF (days)*	24	16	11	10
12-month creatinine	201	141	176	155
1-year graft survival (%)	88	91	86	92

All median values unless stated (percentages) *ANOVA, $P < 0\ 05$

Conclusions: The presence of acute rejection episodes in kidneys retrieved from an NHBD prolongs the duration of DGF but does not appear to influence graft function or graft survival at 1 year.

Vascular

Poster 059

Prospective comparison of conventional treadmill testing with pedal ergometry in patients with suspected claudication

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Aims: In the investigation of claudication, comorbid cardiovascular, neurological and rheumatological disorders mean that some patients are unable to perform conventional treadmill testing The pedal ergometer (Stresst'er) allows limbs to be stressed individually, and ankle pressures recorded, with the patient supine. We aimed to compare this device with the conventional treadmill.

Methods: A prospective study was undertaken, where each patient presenting with a presumptive diagnosis of intermittent claudication was assessed by the same examiner, with each test.

Results: Fifty patients (12 of whom were diabetic) were included, giving a total of 100 limb measurements for each test. Ten patients completed both tests with no exercise-induced ankle pressure changes Three patients were unable to complete either test, despite normal pressure measurements Eleven patients were unable to complete treadmill testing for reasons such as dyspnoea (three), cough (two), dizziness (three), chest pain (two), and unsteadiness (one), despite unchanging pressure values. The same patients completed pedal ergometry testing without a fall in pressure Twenty-six patients had positive testing, 18 of those indicated by both tests, with a mean pressure drop of 74 ± 56·7 mmHg for treadmill testing and 70 ± 49 mmHg for the pedal ergometer ($P = 0{\cdot}79$). Four patients were unable to perform the treadmill test, yet showed pressure changes with pedal ergometry. Three patients showed pressure changes with pedal ergometry, yet none with treadmill testing (false-negatives for the treadmill test), compared with one patient who had pressure changes on the treadmill test, not reproduced by the pedal ergometer.

Conclusions: Pedal ergometry is as sensitive as the treadmill in detecting arterial insufficiency. It is compact, portable and easy to use, and more suitable in a subgroup of patients unable to tolerate conventional treadmill testing.

Poster 060

The PADHOC: a new device for evaluating disease severity in patients with intermittent claudication

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Aims: The treadmill walking test is still the reference method for evaluating the severity of peripheral arterial occlusive disease However, it is thought not to reflect the actual incapacity experienced by the patient in everyday life, so we have used a new device known as the peripheral arterial disease holter control (PADHOC) to evaluate disease severity in claudicants

Methods: Fifty-four patients (29 men, 25 women; median age 67 5 years (range, 48–85)) with duplex or angiographic proven vascular disease of the lower limb were recruited as part of an ongoing prospective trial Each patient estimated their own claudication distance and then completed a standard treadmill test and two physiological walking tests (using the PADHOC device) separated by a 1-min rest. Pre- and post-ABPIs, initial claudication distance (ICD) and maximum walking distance (MWD) were recorded at the time of the treadmill test. ICD, MWD and walking speed were recorded during the two physiological walking tests Disease severity was determined using ISCVS/SVS criteria.

Results:

PADHOC	Median (IQ range)	Treadmill	Median (IQ range)
PICD$_1$	117 m (68–166)	TICD	30 5 m (21–48)
PMWD$_1$	229 m (152–480)	TMWD	52 m (42–100)
PICD$_2$	27 5 m (4–93)	Pre-ABPI	0 75 (0 6–0 88)
PMWD$_2$	122 m (81–245)	Post-ABPI	0 53 (0 32–0 75)

P = PADHOC, T = treadmill, subscripts 1 and 2 indicate first and second PADHOC walking tests, r_s = Spearman rank coefficient

PICD$_1$ and PMWD$_1$ correlated strongly with TICD and TMWD (r_s = 0 60, P < 0·0001 and r_s = 0 71, P < 0 0001 respectively). There was also strong correlation between PMWD$_2$ and TMWD (r_s = 0 55, P < 0·001) Both PMWD$_1$ and PMWD$_2$ correlated with ISCVS/SVS disease classification (r_s = –0·3731, P = 0·006 and r_s = –0·3873, P = 0·007 respectively). Estimated ICD (median, 150 m; IQR, 100–300 m), although correlating with PICD$_1$ (r_s = 0 43, P = 0·002) was significantly overestimated by the patients (P = 0 02, Mann–Whitney U test) Overall patient acceptability of the PADHOC test was better than that for the treadmill test.

Conclusions: The PADHOC system gives an excellent reflection of the functional incapacity suffered by patients with intermittent claudication. It is easy to use, has good patient acceptability and is accurate at evaluating disease severity in patients with intermittent claudication.

Poster 061

Are antihypertensive drugs associated with abdominal aortic aneurysms?

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Aims: To investigate the association between antihypertensive drugs, the risk of developing an abdominal aortic aneurysm (AAA), aortic wall stiffness and change in aortic diameter

Methods: Data on present medication, smoking status and medical history of participants in two population-based aneurysm-screening programmes were collected Aortic elasticity was measured by M-mode ultrasonography. A serum radio-immunoassay of the aminoterminal propeptide of type III procollagen was used to assess collagen turnover

Results: Data from 438 cases with an AAA larger than 29 mm and 5373 controls were analysed. Calcium-channel blockers were independently associated with AAA The relative risk of having an AAA was 2·6 (95% CI, 1 5–4 2) after adjusting for all relevant cofounders The relative risks from other antihypertensive drugs were not increased after adjustment. No significant differences in growth rate were found in cases exposed to any of the main antihypertensive drugs. An increased type III collagen turnover was found in subjects on ACE inhibitors: 4·26 mg L^{-1} (95% CI, 3·73–4·79) compared with those not on ACE inhibitors 3 62 mg L^{-1} (3 49–3 76) No differences in type III collagen turnover were found with the other antihypertensive drugs. The mean aortic wall stiffness for all subjects exposed to calcium-channel blockers, whether with AAA or not, was greater than that of non-exposed subjects: 25 1 (95% CI, 20·0–30·2) *versus* 19 3 (95% CI, 18·1–20·4) (P = 0 002) Mean stiffness in cases on calcium-channel blockers was greater than in nonexposed cases. 28·4 (95% CI, 21 1–35 5) *versus* 23 9 (95% CI, 21 8–25 9), but this was not significant (P = 0 11). By contrast, the mean stiffness for cases on ACE inhibitors was smaller than in cases not on ACE inhibitors: 19·0 (95% CI, 13 9–24 0) *versus* 25·2 (95% CI, 23 0–27·4); however, the difference between all subjects exposed to ACE inhibitors and those not exposed was not significant

Conclusions: Calcium-channel blockers were an independent risk factor for AAAs and were associated with an increased arterial wall stiffness. ACE inhibitors were associated with decreased stiffness and greater collagen turnover No significant effects on growth of small aneurysms were detected.

Poster 062

Is division of the left renal vein ever necessary in the exposure of the juxtarenal aorta?

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Aims: The exposure of the juxtarenal aorta may be facilitated by the division of the left renal vein, although this manoeuvre may be associated with substantial morbidity We prefer to avoid this by the mobilization and retraction of the left renal vein during juxtarenal aortic surgery, and we have retrospectively reviewed our experience using this technique, with the aim of defining the necessity for left renal vein division during aortic surgery

Methods: Complete records for 126 from a consecutive series of 160 patients having undergone abdominal aortic surgery were retrieved and the following data collected operation performed, level of aortic clamp, aortic neck length, management of renal vein.

Results: (a) Twenty-three patients underwent surgery for aortic occlusion, which was juxtarenal in six and infrarenal in 17. One patient required suprarenal aortic clamping. The renal vein required mobilization in five, was not dissected in 16 and was unspecified in two patients No patient required renal vein division (b) Some 103 patients underwent aneurysm repair. (i) Seventy-eight aneurysms were infrarenal. These were all controlled by infrarenal clamping; the renal vein was not dissected in 51, mobilized in 22, divided in one (non-functioning kidney) and unspecified but not divided in four (ii) Twenty-five aneurysms were juxtarenal; 13 required suprarenal clamping, of which the renal vein was mobilized in 11 and divided in two. Twelve were controlled with infrarenal clamps, in which the renal vein was not dissected in one, mobilized in 11 and divided in none.

Conclusions: In infrarenal aneurysm repairs, 28 per cent (22/78) of left renal veins required mobilization to allow crossclamping; when suprarenal aortic clamping is required, renal vein mobilization without division is achieved in 85 per cent (11/13) of cases Left renal vein mobilization is safe, effective and division can be avoided in the majority of cases

Poster 063

Is profunda angioplasty safe? – a 10-year experience

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Aims: In patients with superficial femoral artery occlusion, angioplasty of the profunda femoris artery (the main source of blood supply to lower limb) is not a common technique and the results are poorly documented. The aim of this study was to examine our experience of profunda angioplasty in patients with lower-limb ischaemia.

Methods: During the period 1990–99, 31 patients (median age, 70 years, range, 59–84; men : women = 3 4 1) underwent profunda PTA for lower-limb ischaemia (16 claudicants, group 1; 15 with critical ischaemia, group 2) The results were analysed with respect to technical success, clinical improvement, limb salvage, periprocedural mortality and long-term outcome

Results: The median follow-up was 14 months (range, 0 25–70).

	Technical success	Complications	Pre-ABI	Post-ABI	Improved/ limb salvage	Bypass (within 1 year)	Limb loss	Mortality
Group 1 (n = 16)	15 (94%)	1 (6%)	0 63	0 81	12 (75%)	2 (12 5%)	0	0
Group 2 (n = 15)	15 (100%)	2 (13%)	0 56	0 71	10 (67%)	1 (7%)	2 (13%)	3 (20%)

ABI, ankle brachial index

Conclusions: Profunda PTA is a safe procedure in claudicants and patients with critical ischaemia, with no major morbidity or mortality associated in this series We believe that profunda PTA is an acceptable and safe alternative to open profundaplasty in selected patients

Poster 064

Maintenance of patency following remote superficial femoral artery endarterectomy (RSFE)

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Aims: RSFE is a minimally invasive means of superficial femoral artery endarterectomy It comprises a single groin incision and securing of the distal cut end of atheroma with an intraluminal stent. The aim of this study was to determine the medium-term results of RSFE.
Methods: Stenosis development and patency of 25 RSFEs were compared with 25 randomly selected *in situ* vein bypasses with similar follow-up (18–33 months).
Results: Following RSFE, 17 stenoses were identified by duplex surveillance. Half of those arteries patent at 1 year had stenoses. Angioplasty (PTA) was carried out for 11 stenoses. Four stenoses developed more than 12 months following RSFE. One patient died and nine arteries occluded during follow-up Primary and primary-assisted patency at 18 months were 31 per cent and 63 per cent respectively. By contrast, six stenoses were identified in 25 *in situ* grafts, all within 1 year. Four PTAs were carried out Three grafts occluded Excluding cost of 3-month duplex surveillance, the cost of maintaining RSFE patency was approximately four times that of maintaining *in situ* bypass patency.
Conclusions: The initial cost advantage of RSFE is offset by the increased costs of maintaining patency. Duplex surveillance probably needs to be continued indefinitely.

Poster 065

Is minimally invasive saphenous vein harvesting worthwhile?

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Aims: To evaluate prospectively the minimally invasive technique of saphenous vein harvester (SVH) compared with the skin bridge technique (SBT) for harvesting the long saphenous vein in patients undergoing femorodistal reconstruction.
Methods: Patients undergoing femorodistal reconstruction were randomly allocated to either SVH or SBT for vein harvesting Both intraoperative and postoperative data were collected. Graft patency was assessed at follow-up using duplex scan. Statistical analysis was performed using the Mann–Whitney *U* test
Results: Fourteen patients were recruited, with seven in either group. Both groups were matched for age and sex. The SVH group had a smaller number of skin incisions (3 *versus* 4, $P = 0\ 02$) and the total length of the incisions was shorter (25 cm *versus* 48 cm, $P = 0\ 005$) The length of vein graft harvested was comparable (47 cm *versus* 57 cm, $P = 0{\cdot}31$). The number of injuries to the vein graft was higher in the SBT group than in the SVH group (1 *versus* 2, $P = 0{\cdot}02$). The number of side branches torn (2 *versus* 2, $P = 0{\cdot}90$) and the vein harvest time (53 min *versus* 55 min, $P = 1\ 00$) were both comparable. However, the vein preparation time was shorter for the SVH group (8 min *versus* 17 min, $P = 0{\cdot}01$). The early wound complication rates were comparable, with one patient in each group with wound dehiscence. The mean hospital stay was 10 ± 1·3 days in the SVH group and 10·1 ± 1·1 days in the SBT group. One graft failed in each group.

Conclusions: The minimally invasive technique of SVH allowed harvesting of the saphenous vein via shorter skin incisions without compromising the quality of the graft. A larger number of patients are required to show further benefits.

Poster 066

Results of an aggressive limb salvage policy in patients with infragenicular arterial occlusive disease and critical limb ischaemia

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Aims: To analyse the results of an aggressive limb salvage policy using distal vessel exploration, on-table digital subtraction angiography (DSA) and preferential use of reversed long saphenous vein (LSV) (including harvesting from both lower limbs) for patients with below-knee arterial occlusive disease and critical limb ischaemia.
Methods: Details of 146 cases of critical limb ischaemia in 136 patients of median age (range) 73 years (41–93) were collected retrospectively from the vascular audit database and patient case notes, and analysed.
Results: Eight-six cases were identified as having significant below-knee arterial occlusive disease on preoperative angiography Of these, 26 (30 per cent) underwent primary limb amputation (indications included unreconstructable vessels on angiography (42 per cent), irreversible tissue loss (54 per cent) and patient comorbidity (30 per cent)). Fifty-eight patients (67 per cent) underwent below-knee vessel exploration with on-table DSA in 46 patients (53 per cent) to visualize the distal runoff. Eight patients who had exploration (14 per cent) had vessels unsuitable for reconstruction, leading to lower-limb amputation ($n = 6$), forefoot amputation ($n = 1$) and death ($n = 1$). Fifty patients (58 per cent) underwent distal arterial reconstruction, including 10 below-knee femoropopliteal grafts (nine reversed LSV, one PTFE) and 40 femorodistal grafts (nine PTFE, one *in situ* LSV, 30 reversed LSV). In 13 cases, an adequate length of vein was obtained by anastomosing two lengths of vein, one from each leg (femoropopliteal, $n = 3$; femorodistal, $n = 10$) Completion digital subtraction angiograms were performed in 49 reconstructions (98 per cent). Cumulative limb survival for those undergoing revascularization was 90 per cent and 81 per cent at 1 and 6 months respectively. Complications included early graft thrombosis ($n = 8$), leading to limb amputation (above-knee, $n = 3$; below-knee, $n = 1$), anastomotic leak ($n = 1$), PTFE graft infection and excision ($n = 1$), MRSA wound infection ($n = 8$), other wound infection ($n = 8$) and wound debridement ($n = 6$). Two of 13 cases (15 per cent) where vein was harvested from the contralateral leg were complicated by wound infection. In-hospital mortality in patients undergoing attempted reconstruction was 16 per cent ($n = 9$).
Conclusions: High rates of limb salvage can be achieved in patients with critical limb ischaemia secondary to distal occlusive disease. This is associated with a high, in-hospital mortality, however

Poster 067

A decade of PTFE with venous collar

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Aims: To assess the mid-term patency of polytetrafluoroethylene (PTFE) femoral below-knee popliteal and crural bypasses with venous collar, performed for critical limb ischaemia in one
Methods: Some 142 PTFE below-knee bypasses with venous collar were performed in the 10-year period 1989–98 (130 for critical ischaemia and 12 for short-distance claudication), with complete data available on 118

procedures. A total of 114 patients (76 men and 38 women, age range, 49–89, median age, 59) were reviewed Graft occlusion was confirmed by either duplex or angiography in all cases. Using life table analysis with a Cox's proportional hazard model, the following variables were analysed to ascertain effect on patency: age, diabetes, hypercholesterolaemia, grade of surgeon, site of bypass (below-knee popliteal/crural) and use of warfarin

Results: Life table analysis showed graft patency and limb salvage rates as follows

	1 month	6 months	12 months	18 months	24 months
Patency (95% CI)	85% (77, 90)	69% (59, 77)	60% (50, 69)	42% (32, 52)	27% (18, 36)
Limb salvage	95% (87, 97)	84% (75, 90)	80% (70, 87)	64% (52, 74)	49% (36, 60)

The following risk factors associated with occlusion rate were individually analysed

	Age	Diabetes	↑Lipids	Grade (SR/Con)	Crural bypass	Warfarin
Relative risk	1 13	1 42	0 72	1 65	0 94	0 68
(95% CI)	(0 99, 1 29)	(0 87, 2 33)	(0 39, 1 33)	(1 04, 2 61)*	(0 54, 1 63)	(0 44, 1 04)

*$P<0$ 05

Conclusions: The mid-term survival rate of PTFE grafts with venous collars justifies its role in limb salvage in patients with critical limbs A significant increase in occlusion rate was found where the procedure was performed by a surgical trainee, the most likely estimate of the effect of postoperative warfarin is a reduction in risk of graft occlusion of 32 per cent.

Poster 068

Audit of the management of major limb amputation in a university teaching hospital

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Aims: Patients undergoing major limb amputation have better outcomes when managed by specialist vascular surgeons The aims of this study were to review the management of amputation in a specialist vascular unit and to assess the indications for amputation instead of reconstruction.

Methods: Vascular audit data and patients' case notes were reviewed retrospectively. Eighty-nine consecutive major limb amputations in 82 patients of median age (range) 72 years (31–94), performed over a 3-year period, were reviewed. Sixty-one per cent of patients were diabetic ($n=50$) and 10 per cent were undergoing renal replacement therapy ($n=8$)

Results: Forty-eight per cent had above-knee amputations ($n=43$), 51 per cent had below-knee amputations ($n=45$) and 1 per cent had through-knee amputation ($n=1$) The indication for amputation included critical limb ischaemia (85 per cent), irreversible acute limb ischaemia (3 per cent), irreversible tissue loss (11 per cent) and complication of arterial surgery (4 per cent). Ninety-four per cent of cases ($n=84$) were reviewed prior to amputation by a consultant vascular surgeon, and 84 per cent ($n=75$) of cases were performed or supervised by a consultant vascular surgeon In patients having limb amputation where the indication was irreversible critical ischaemia ($n=76$), 66 per cent had primary amputations ($n=50$), 22 per cent followed bypass graft failure ($n=17$), and 12 per cent followed vessel exploration and operative angiography without arterial reconstruction ($n=9$). Thirty-two per cent ($n=24$) of patients with critical ischaemia had amputation without prior angiography. This was because of a nonviable limb in 25 per cent (following graft excision/failure with no option for reconstruction ($n=5$), irreversible tissue loss ($n=11$), gas gangrene ($n=3$)), the use of duplex imaging in 3 per cent ($n=2$) and patient comorbidity in 4 per cent ($n=3$). A further 26 per cent ($n=20$) underwent angioplasty without clinical improvement Following major limb amputation, 6 per cent had secondary healing following wound debridement ($n=5$), and 8 per cent underwent revision to a higher level ($n=7$). In-hospital mortality was 27 per cent ($n=22$)

Conclusions: These data show that our practice conforms to national guidelines, with a consultant-based service (preoperative assessment and attendance at operation) This practice has produced low levels of secondary healing and re-amputation

Poster 069

Transaxillary rib resection for thoracic outlet syndrome

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Aims: To compare short-term clinical outcome following transaxillary rib resection for thoracic outlet syndrome (TOS) with a long-term assessment conducted by telephone questionnaire

Methods: Over a 10-year period, 61 patients underwent 83 transaxillary rib resections for TOS. A retrospective review of clinical findings, operative details and outpatient records of the clinical outcome was undertaken. All patients were telephoned by an independent observer and asked to complete a telephone questionnaire regarding long-term outcome

Results: Postoperative outpatient assessment at a median of 6 months recorded that 91 5 per cent of patients had improved, of whom 61 5 per cent were symptom-free. Some 61 per cent of patients were available for the telephone questionnaire at a median follow-up of 4 years, 73 per cent reported an improvement in symptoms, with complete resolution in 59 per cent. Six patients reported a temporary improvement following surgery Fifty-nine per cent had returned to full activity, with 62 per cent perceiving an overall benefit from the procedure.

Conclusions: Initial outpatient assessment was more optimistic than long-term follow-up with telephone questionnaire While the development of recurrent symptoms might partially explain this, observer bias may also be an important factor. Therefore, caution should be exercised when counselling patients on the expected outcome of this procedure

Poster 070

Two-point discrimination aesthesiometry in patients with the hand–arm vibration syndrome

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Aims: The hand–arm vibration syndrome (HAVS) is becoming increasingly seen in the outpatients of many vascular surgeons. The vascular aspect of the disease is well recognized but, as yet, the sensorineural dysfunction experienced by sufferers is less recognized Therefore, we aimed to determine the sensorineural dysfunction experienced by patients with HAVS, using a wheel aesthesiometer.

Methods: We examined 83 patients (median age, 48 years, range, 27–75) diagnosed as having HAVS and 30 age-matched controls (median age, 47 5 years; range 20–59 years) Of the 83 patients with HAVS, 68 were graded as stage 3 on the Stockholm Workshop (SW) scale, nine as stage 2 and six as stage 1. Two-point discrimination (TPD) aesthesiometry was performed three times on each digit of both hands. A wheel aesthesiometer was used and the subject's finger was first rested against a single ridge. On turning the wheel, the ridge initially diverges, reaching a maximum distance between the ridges of 8·74 mm at 180° round the wheel On further turning of the wheel, the two ridges converge into one The subjects were initially asked when they first felt two ridges (two points) and then when they felt one ridge again (one point). Mean threshold values were then calculated for each hand in millimetres

Results: Median (IQ range), statistical analysis by Mann–Whitney *U* test

	HAVS	Controls	*P* value
Right two-point	5 24 (4 03–6 16)	2 62 (2 08–3 09)	<0 001
Right one-point	2 11 (0 85–3 25)	2 59 (2 16–3 04)	0 17
Left two-point	5 11 (3 76–6 05)	2 92 (2 58–3 15)	<0 001
Left one-point	1 94 (0 96–2 96)	2 83 (2 56–3 24)	<0 001

Subjects classed as stage 3 on the SW scale had significantly higher right and left two-point thresholds compared with those subjects classed as stage 2 or 1 on the SW scale ($P<0{\cdot}01$). No significant difference was observed in threshold values when comparing dominant and non-dominant hands
Conclusions: Patients with HAVS have significantly impaired sensorineural function that deteriorates as disease severity increases. Aesthesiometry is a simple tool that can be used in the assessment of sensorineural dysfunction in patients with HAVS.

Poster 071

Duplex-guided thrombin injection as a treatment for iatrogenic femoral artery pseudo-aneurysms: an effective nonoperative technique in anticoagulated patients

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Aims: To evaluate the efficacy and safety of an alternative nonoperative method for treating postcatheterization femoral artery pseudo-aneurysms in patients who are anticoagulated and nonanticoagulated.
Methods: Twenty-seven patients with symptomatic pseudo-aneurysms of the femoral artery secondary to radiological catheterization were included (mean maximal diameter, 3 4 cm, range, 2 22–8; median duration from onset, 7 days; range, 2–80). Following measurement of cavity dimensions and size of the neck and communicating tract, 200–2000 units of thrombin (1000 units mL^{-1}) in a titrating dose were injected into the centre of the cavity under duplex guidance, using a 22 G needle to induce thrombosis, with no sedation or anaesthesia required. The distal circulation was assessed before and following injection to exclude thrombus propagation.
Results: Successful rapid thrombosis was induced in all 27 case (100 per cent), with no immediate or mid-term procedure-related complications or recurrences at 6 weeks. 17/27 (63 per cent) of the patients were therapeutically anticoagulated at the time and following the procedure with either heparin or warfarin (median, APTT = 82 s; INR = 2·3). This did not alter the success of the procedure There was no difference between the anticoagulated and nonanticoagulated patients in the median size of the pseudo-aneurysm or the thrombin dose required to thrombose the false aneurysm ($P=0$ 65; $P=0{\cdot}43$ respectively (Mann–Whitney *U* test)).
Conclusions: This is a simple, quick, painless, safe and effective technique for treating both acute and chronic femoral artery pseudo-aneurysms of all sizes. It has benefits over ultrasound-guided compression, particularly in patients taking concurrent anticoagulation where compression is painful, prolonged and often less successful

Poster 072

A stitch in time: the use of vascular staples to close carotid arteriotomies

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Aims: We present a prospective randomized trial of the previously unreported technique of closing the carotid artery, in patients undergoing carotid endarterectomy, with vascular staples We postulate that this will result in a significant reduction in the carotid artery crossclamping time, so reducing the risk of cerebrovascular incidents in these patients
Methods: Thirty consecutive patients undergoing carotid endarterectomy under the care of a single surgeon were randomly assigned to have their carotid arteriotomy either closed by a standard continuous proline suture or with vascular staples. Shunts were used in all patients. The total non-shunt crossclamp time was recorded for all patients. The patients were all followed up with carotid duplex scan at 3 and 9 months after the operation.
Results: There were 15 patients in each of the two groups, 11 men and four women, of average age 74 (range, 60–81) and average stenosis of 76 per cent (stapled); and 10 men and five women of average age 70 (range, 48–83) and average stenosis of 76 per cent (sutured). In the suture group, the average total crossclamp time was 229 s (range, 189–345) compared with 144 s in the stapled group ($P<0$ 0005). There were no strokes in either group In the sutured group, two patients developed postoperative wound haematomas. Two patients suffered a period of confusion and reduced conscious level that lasted less than 6 h after the operation. There was one case of temporary 12th nerve neuropraxia. In the stapled group, there was one death and a wound haematoma in the same patient The patient died of pneumonia 7 days postoperatively. One, previously well, 80-year-old patient was found to be confused at the 3-month follow-up. All other patients were alive and well at 3 and 9 months follow-up, and there were no significant restenosis in either group.
Conclusions: Staple closure of the carotid artery is quick, easy and significantly reduces carotid artery crossclamp time, with no significant increase in morbidity or mortality Ultimately, a decrease in cerebral ischaemic time may reduce stroke rate in carotid endarterectomy patients but more patients will need to be studied to prove this.

Poster 073

Development of a tissue-engineered small-diameter vascular graft

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Aims: To tissue-engineer a function endothelium on a 'living' collagen matrix supported by a polyester scaffold
Methods: Porcine aortic smooth muscle cells (SMCs) were used to contract collagen onto a standard polyester graft scaffold within specially designed bioreactors. The collagen matrix was preconditioned within a pulsatile flow circuit at a constant mean pressure, temperature and pH Porcine aortic endothelial cells (ECs) were then seeded at a cell density of 2×10^5 cells cm^{-2}. Tissue plasminogen activator (tPA) level was assayed to assess EC functionality Environmental scanning electron microscopy was used to determine the extent of the endothelial lining, while confocal microscopy assessed cellular viability.
Results: Collagen contraction occurs rapidly within the first 5 days, resulting in an 80 per cent reduction in the thickness of the external matrix. Elongated SMCs were seen both within the weave of the polyester fibres and distributed throughout the external matrix. ECs adhered in good numbers to the luminal surface and secreted tPA. Both SMCs and ECs showed minimal uptake of propidium iodide when viewed by confocal microscopy No significant delamination of the collagen matrix was noted when the graft was subjected to pressures in excess of 200 mmHg
Conclusions: We have demonstrated the feasibility of producing a functional endothelium on a 'living' collagen matrix Further work to assess its antithrombogenic properties and structural integrity *in vivo* is in progress

Poster 074

Deficiency in interleukin-2 production by peripheral blood mononuclear cells in patients with abdominal aortic aneurysms

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Aims: Cytokine-induced tissue inflammation participates in the pathogenesis of abdominal aortic aneurysms (AAAs). The aim of this study was to quantify intracellular T cells cytokines in patients with atherosclerotic AAAs.
Methods: We studied healthy controls (*n* = 11; age, 60 ± 6·1 (mean age ± s.d.)), and patients with elective infrarenal AAAs (*n* = 6; age, 69 ± 8·6). Peripheral blood mononuclear cells (PBMCs) were isolated using a Ficoll density centrifugation technique. We stained for surface markers (CD4+, CD8+) and intracytoplasmic cytokines (interleukin-2 (IL-2), interleukin-4 (IL-4), gamma-interferon (IFN-γ)) with monoclonal antibodies. Single-cell analyses were performed with flow cytometry, which offers the advantage of representing results as a proportion of cells expressing the specific cytokine rather than of the total amount of cytokine produced.
Results: Results are represented as means ± s.e.m.

	IL-2 (CD4+ and CD8+)	IL-4 (CD4+ and CD8+)	IFN-γ (CD4+ and CD8+)
Controls	4·72 ± 0·18	0·38 ± 0·02	5·49 ± 0·10
AAAs	3·00 ± 0·36*	0·23 ± 0·02	7·40 ± 0·91

Mann–Whitney *U* test *$P < 0·005$

Subgroup analysis demonstrated that production of CD4-IL-2, CD8-IL-2 were decreased in AAA patients, while there were no significant changes in CD4-IFN-γ, and CD8-IFN-γ, CD4-IL-4 or CD8-IL-4 production.
Conclusions: This is the first study to suggest that patients with AAA may have impaired Th$_1$ cytokines (such as IL-2) production. This may be important for local lipid metabolism and plaque stability. Increasing production of Th$_1$ cytokine by immunomodulation may, therefore, have prophylactic or therapeutic potentials in AAAs.

Poster 075

Platelet activation occurs during bypass surgery for critical limb ischaemia and remains elevated postoperatively

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Aims: Platelet activation represents the final common pathway leading to thrombosis and graft occlusion after bypass for critical limb ischaemia. This study investigated platelet activation status in patients before, during and after femoropopliteal bypass.
Methods: We investigated 14 patients undergoing femoropopliteal bypass for critical limb ischaemia. Blood was taken preoperatively and at the following time points: incision, dissection, ischaemia, reperfusion and 24 h after surgery. Fifteen patients were studied a mean of 22 months after bypass surgery. Fourteen matched patients, without vascular disease, were used as controls. Flow cytometric analysis was performed using monoclonal antibodies: PAC-1 for activated GPIIb/IIIa; and CD62P for P-selectin. Platelet aggregation, spontaneous and after adenosine diphosphate (ADP) enhancement, was measured using a turbidometric method. Data are expressed as mean (± s.e.m.) and statistical analysis was performed using the Mann–Whitney *U* test.
Results:

	Spontaneous platelet aggregation (%)	Aggregation after ADP enhancement (%)	PAC-1 expression	P-selectin expression
Controls	31·5 (±3·6)	43·6 (±6·1)	11·35 (±1·85)	3·96 (±0·99)
Preop	36·3 (±2·9)	61·3 (±7·3)*	20·47 (±3·32)	2·58 (±0·41)
Incision	24·8 (±4·3)	74·5 (±8·1)*	11·09 (±4·15)	1·75 (±0·94)*
Dissection	22·0 (±3·8)	75·3 (±7·8)*	12·75 (±4·73)*	3·68 (±1·90)*
Ischaemia	26·2 (±4·0)	77·5 (±6·1)*	17·79 (±5·40)	4·58 (±2·40)
Reperfusion	23·5 (±4·1)	71·9 (±8·6)*	5·39 (±2·03)*	1·73 (±0·77)*
24 h	37·2 (±5·7)	77·0 (±6·1)*	24·17 (±5·15)*	7·40 (±2·52)
Post-bypass	36·5 (±5·2)	87·9 (±2·8)*	29·44 (±4·14)*	6·75 (±1·92)

*$P < 0·05$, Mann–Whitney *U* test

Platelet activation was similar between controls and the patient baseline. Activation decreased at incision but platelets remained highly reactive. Platelet aggregability increased during dissection and the ischaemia phase, but significantly decreased during reperfusion. Platelet aggregability and degranulation increased after surgery and remained elevated at 24 h and a mean of 22 months after bypass grafting.
Conclusions: Platelet aggregability significantly increased during bypass surgery and remained activated subsequently, so increasing the risk of thrombotic graft occlusions. Long-term antiplatelet agents may be effective in minimizing this hazard.

Poster 076

More venous leg ulcers are healed by three-layer paste than by four-layer bandages: a randomized, controlled, prospective study

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Aims: To compare the time to total healing in two groups of patients treated with three-layer or four-layer compression bandage regimens in a random prospective manner.
Methods: Some 144 patients were studied: 71 had three-layer paste bandages and 73 had four-layer bandages. All ulcers were stratified and randomized within one of three size groups. Patients with ulcers of less than 0·25 cm^2 or greater than 100 cm^2 were excluded. Patients with diabetes, sickle cell disease, arterial disease (ankle brachial index , 0·9) and those with positive autoimmune serology were not entered into the study. All study subjects were followed up for 1 year. A venous aetiology was confirmed on completion of healing using colour flow duplex scanning, foot volumetry and ascending venography to demonstrate abnormal calf pump function. Statistical analysis was performed using χ^2 tests and Kaplan–Meier survival curves.
Results: At 1 year, 46 of the three-layer paste-bandage-treated and 39 of the four-layer-bandage-treated patients were healed. Twenty-two patients were excluded or withdrawn from the three-layer group and 23 patients from the four-layer group. Reasons for exclusion or withdrawal included lack of patient compliance, bandage intolerance and failure of attendance to follow-up. Allowing for exclusions or withdrawals, 46/49 (94 per cent) of the three-layer-bandage-treated patients and 39/50 (78 per cent) of the four-layer-bandage-treated patients healed ($P < 0·05$). Large ulcers healed significantly more slowly than smaller ulcers. Three-layer paste bandages healed 9/12 (75 per cent) and four-layer bandages healed 7/14 (50 per cent) of large ulcers.
Conclusions: Three-layer paste bandages are significantly more effective at healing venous leg ulcers than are four-layer bandages.

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Leading article

BJS in the new millennium

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As we look to the new millennium most of us will be taking stock of our situation, of our successes and failures, and will be reflecting on what has passed and on our future hopes. Certainly this is so at the *British Journal of Surgery*. The first issue of the Journal appeared in July 1913 and it has been published without interruption to the present day, with Volume 87 in the year 2000. As early as 1936 the Journal had achieved its peak circulation of 9100 and contained 1024 pages. It has remained a prominent force in medical publishing since then; in 1999 it had a circulation of 7500 and contained 1616 pages, an increase in size of 58 per cent.

BJS has evolved over the 20th century and the rate of change has never been so great as in recent years. Ten years ago (1989) saw 249 original articles, 49 leaders and reviews, and 88 short reports published, whereas in 1999 the respective figures were 214, 48 and 13. It is gratifying to note that the number of randomized clinical trials increased from three to 13 per annum. The Editors firmly believe that the more exacting editorial policy of recent times (especially with respect to reducing the number of short reports) has produced a leaner and fitter Journal; a vibrant, viable product for the next century. External confirmation of this comes from the Journal's impact factor which in 1998 (the last year for which the value can be calculated) was an all time high of 2·38. In terms of impact factor, *BJS* ranks first in the world among non-American peer-reviewed general surgical journals, and fourth if USA-based publications are included. It has an excellent cited half-life of 7·7 years.

Of course in the modern era there is more to medical publishing than the management of a paper journal. The scientific publishing community in general and *BJS* in particular have not been blind to the charms of the personal computer. *BJS* first appeared on CD-ROM in 1996 and this has now been superseded by its appearance on-line in the year 2000. The Journal also has its own website (www.bjs.co.uk) where one can check on forthcoming publications. The website also contains our Scientific Surgery Archive, in which is lodged an up-to-date record of randomized clinical trials, systematic reviews and meta-analyses gleaned from the published English-language literature, which the Editors believe may be of interest to our surgical readership. The *BJS* website certainly seems popular, with the number of overall site hits increasing from about 2000 in January 1999 to over 4000 in August 1999; the home page in particular has over 1000 hits per month. In two search engines (Alta Vista and Lycos) the *British Journal of Surgery* home page is one of the top three surgical titles. More and more referees are taking advantage of completing report forms electronically and we are attempting to make this process more user friendly.

Ethical issues have been with the Journal since its inception. In 1916, for example, Sir William Watson Cheyne simultaneously published the same article in the *British Medical Journal*, the *Lancet* and the *British Journal of Surgery*. The pressures to publish clinical and research work increase each year as new techniques and technologies are introduced into surgical practice. Basic surgical research continues as an important component of surgical training and everyday practice. Publication performance is often linked with promotion within institutions, and institutions may receive proportions of funds commensurate with departmental productivity; an example is the UK Research Assessment Exercise. Pressures such as these may contribute to the incidence of publishing misdemeanours. Perhaps electronic journals and cross-checks have made us more aware of these problems. They may have occurred previously at the same rate but were occult.

BJS has been disturbed to uncover several publication misdemeanours (plagiarism, attempted dual and salami-slice publication, misleading or incomplete data, etc.) and readers will have seen editorial notices and examples of these upsetting situations. The Journal places emphasis on publication ethics in terms of probity and totally endorses the Committee on Publication Ethics (COPE) Guidelines on 'Good Publication Practice'. These guidelines can be seen on www.publicationethics.org.uk and are commended to our readers. The Journal is a member of COPE and fully endorses its activities.

The Editors are ethically and morally obliged to pursue and report misconduct, where appropriate, to employers and, in extreme cases in the UK, to the General Medical Council. The Journal is supported by professional legal advice and often makes joint declarations with other journals. Publication misdemeanour may occur through naivety, ignorance and/or genuine error. In an attempt to be constructive, the issues of the year 2000 will carry leading articles designed to help those about to embark on a writing career and to help refresh the memory of the others. These

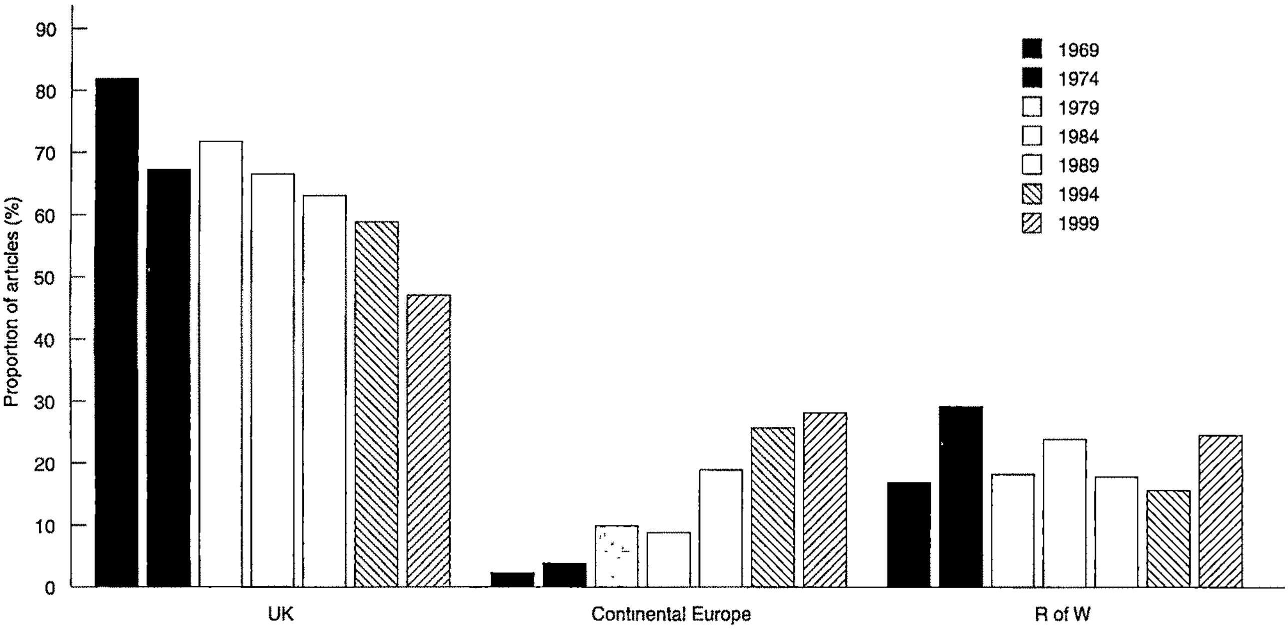

Fig. 1 Proportion of articles published according to geographical origin and year (calculated from April, May and June issues). R of W, rest of world, excluding Europe

articles will be written by the Editors and international authorities. They will deal with all the steps of the publishing process, including why we do it, how to do it, the referee and editorial process and, sadly, how to cope with a rejected article. Where appropriate, COPE guidelines will feature alongside the relevant articles. We hope you enjoy this series of papers.

The Editors are pleased to bring to the attention of readers the generosity of the British Journal of Surgery Society which returns considerable sums back into the surgical community in the form of research bursaries, travelling fellowships and prizes. Some notable donations were the £350 000 towards the Education Centre and the Association of Surgeons Rooms in the Royal College of Surgeons of England in 1998, and in 1999 £30 000 towards research bursaries, over £30 000 to sponsored subscriptions and £17 000 in overseas travelling fellowships, to mention but a few.

Where do we go from here? *BJS* will endeavour to retain its present status as the premier general surgical journal in Europe. Indeed, its European commitment has increased unremittingly over the past 30 years (*Fig. 1*), a process that shows little sign of slowing. UK-based publications filled 82 per cent of the Journal's pages in 1969, but by 1999 this had fallen to 47 per cent. On the other hand, work from the rest of Europe made up 2 per cent of the Journal in 1969 and 28 per cent last year. The world outside Europe accounted for between 16 and 29 per cent per annum over this time period, without any discernible trend. The majority of *BJS* publications now originate outwith the UK and, on current trends, continental Europe will be the main source of published material in this Journal within a decade.

The 'Europeanization' of *BJS* has also been reflected in recent years by joint ventures with a variety of European partners, such as Eurosurgery, the Surgical Infection Society (Europe), the European Society of Surgical Research, *Annales de Chirurgie* and *Der Chirurg*. *BJS* also has a special relationship with several national societies whose annual subscriptions include the cost of the Journal for their members. These societies regard *BJS* as their preferred means of publishing abstracts and papers around the time of their scientific meetings. The latest organization to affiliate in this way is the Association of Surgeons of the Netherlands (as of January 2000). The Editors expect a mutually rewarding publishing future with our Dutch colleagues and we take this opportunity of welcoming them to the Journal. We are sure their representatives will have an important role to play on our Editorial Committee and Council in the new millennium.

Acknowledgement

The authors thank Miss E. Lawrence for producing the data used in *Fig. 1*.

Surgical publishing

Why should a surgeon publish?

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> 'Writing was everything' – Alfred Kazin.

For the majority of surgeons writing is not everything and some will not write at all during their career. Exhausted by attempts at alleviating suffering and the increasingly difficult tasks of bread-winning and administrative duties, most surgeons will leave writing for others. We know, however, that there are many surgeons 'out there' who are young and eager to write, but do not have the slightest idea how to begin. If you are an established academic surgeon, this leader, the first in a new series, may not be for you.

This series is, however, aimed at surgeons who have that novel idea, observation or message waiting to be published but do not know the route leading to successful publication (and thereby dissemination) in the pages of a surgical journal. You wish to share a valuable experience with the rest of the surgical world but there is no one to guide you.

Some 'How to Write/Publish' books for scientists and medical professionals are available but to date none has ever been dedicated to surgeons. We intend to attempt to do this in each issue of the Journal during the next 12 months by providing leaders on different topics (*Table 1*). We will not teach you statistics, nor will we tutor you on the correct usage of English. We intend to be simple and brief, and to use practical examples from daily life. We sincerely hope that after reading this series you will be ready to write your own scientific or clinical surgical papers; not those that are regularly rejected but those that will be published in reputable journals.

Table 1 An outline. How to write and publish for surgeons

Introduction – Why should a surgeon publish?	M. Schein J. R. Farndon A. Fingerhut
What can a surgeon publish?	R. O'Connell
Where can the surgeon publish?	M. Schein A. Fingerhut
Generating an idea. Will it be publishable?	M. Sarr
What the editors and reviewers want to see?	C. Organ
On getting started	D. Alderson
Writing the manuscript	S. A. Wells
The 'foreign' author	M. Rothmund A. Fingerhut
The final product	J. A. Murie
Politics in surgical publishing	J. R. Farndon L. Rikkers
The ethics of publishing	M. Farthing
On the editor's desk	J. R. Farndon J. A. Murie
The rejected article	J. J. Earnshaw P. J. Guillou
Epilogue and conclusions	J. R. Farndon M. Schein A. Fingerhut

Why should a surgeon publish?

'Reading maketh a full man, conference a ready man and writing an exact man,' said Francis Bacon. The reasons for writing and publishing are both egoistic and altruistic (*Table 2*). Being altruistic may eventually influence your ego as well!

Table 2 Why should a surgeon publish?

Egoistic motives	Altruistic motives
Academic promotion	Dissemination of knowledge
Professional promotion	Research selectivity
Improve knowledge and judgement	
Being 'famous'	
Develop professional contacts	
Financial gain	

Egoistic motives for writing and publishing

Academic promotion

The dictum of 'publish or perish' is still firmly entrenched in academia. It is difficult to climb the academic ladder without a certain number of papers on your curriculum vitae. To progress academically to whatever academic title you aspire, your published output must constantly grow in number and quality. Obviously publications are not the only key to promotion but, as Bulwer-Lytton said, 'The pen is mightier than the sword'. In some countries, the number and quality of publications (graded on where the paper was published and how many times it has been cited) have a direct influence on academic ascension.

Professional promotion

This commonly follows academic promotion and vice versa. Let us say you are a resident or registrar seeking a prestigious fellowship or additional training in a centre of excellence, then your chances of competing successfully may be much better if only two to four relatively minor papers decorate your curriculum vitae. The mere fact that you have written and published signals to your potential employers that you are a 'thinker', interested in what you do and eager to share your experience with others. It will also suggest that you will continue to contribute academically in your new position. Do understand that writing and publishing is not limited to the 'academic surgical world'. Excellent and pioneering papers were and still are produced by astute clinicians from the non-academic surgical community. Well published 'non-academic' surgeons are respected by their peers, and publications add stature to their personalities and professional respectability. Who will you tend to believe: the surgeon who has published her results in a respectable journal or the one who rises at a meeting and says, 'I did 100 such cases with excellent results but I simply never found time to write and publish'?

Improve knowledge and judgement

Most of the authors of this series of leaders will have separately published 100–200 articles each. Any such paper written and published, be it a case report or a prospective randomized trial, contributed to, and added depth to, knowledge and understanding of the topic around which the publication revolved. The process also widens and deepens your own acumen, and the more you know the better you can serve your patients and yourself. You will never forget a topic about which you have written. Horace said, 'The secret of good writing is sound judgement', but good writing also provides you with the judgement. It allows you to analyse what you did, reflect on it and do better the next time.

Being 'famous'

As John Kenneth Galbraith said, 'Authorship of any sort is a fantastic indulgence of the ego'. The satisfaction one feels seeing a name in print is human and so is the pleasure derived from being quoted by others. A well published surgeon soon becomes 'famous': not only a prophet in his home town but perhaps worldwide. You could be the best surgeon in town but only after your results are published will you also be recognized in the capital and beyond.

Don't we all want to be 'significant' in one way or another? As surgeons we achieve a certain measure of significance through healing. But the subjects we heal are temporary residents on earth. Publishing, if 'significant', may provide us with the sense of the much desired 'significant permanence'. Would anyone remember today the name of Rudolf Nissen had he not published?[1] As Emerson wrote, 'He that writes to himself writes to an eternal public'.

Develop professional contacts

'The universal object of men of letters is reputation,' said John Adams. The more you write the greater will be your reputation, which in turn makes you attractive to people of reputation across the world. The international professional contacts which develop increase your perspective and ability to publish, and become the basis for further exchanges and improvement of the quality of your work. The Medical Club is truly international with no joining requirements and no membership fees. The bonds of international friendship through authorship and the medical profession are strong and enriching of life itself.

Financial gain

'Money, money, all is money! Could you write even a penny novelette without money to put heart in you?' wrote George Orwell. This, however, is not exactly true for the writing surgeon. Promotion and fame, which come with 'being well published', may eventually help you to acheive a better-paid position. But practically speaking, the time spent writing, if dedicated to fee-paying clinical work, would be much more profitable. Satisfaction, however, cannot always be measured in currency!

Altruistic motives for writing and publishing

'You don't write because you want to say something; you write because you've something to say,' wrote Scot Fitzgerald. This is also the main reason for you to write – to share your finding, experience and thoughts with the surgical community. The main purpose of professional publishing is to disseminate knowledge. What exactly should be written and published are subjects of future leaders in this series (*Table 1*). All we need to mention here is that surgeons have a certain degree of moral obligation to publish any significant novel observation, be it 'positive' or 'negative', a 'success' or 'failure'.

In some national academic settings, research output and quality are measured and these measures play upon the amount of resource given by government to the university or college. Your productivity therefore feeds directly on to the financial well-being of your institution. Such a model is the Research Assessment Exercise in the UK. In some institutes research productivity and publishing activity are measured, and will determine proportions of your salary.

The pressures to publish are sometimes inordinate. We would like to think that publishing misdemeanours are mainly due to these pressures. We acknowledge that other factors may play a part in this process which causes inconvenience, embarrassment and undue work in those searching catalogues or indices. Readers will have seen this Journal's firm stance on these issues and the editors of the *BJS* are committed members of the Committee on Publication Ethics (COPE). The Journal is pleased to publish COPE guidelines as appropriate link subjects are encountered in this series of leading articles.

Not everyone shares these sentiments and there are those who think that there are too many journals and too many 'non-significant' publications. Some suggest limiting surgical output to a few top journals, 'supplied' by top academicians[2]. We contend, however, that such a non-egalitarian publishing world, if ever allowed to prevail, would produce a false and biased image of surgical practice, and show surgery as practised in highly sophisticated ivory towers. That surgical writing should not only be limited to a few aristocrats is reflected today on the Internet, as more surgeons flock to its surgical sites in order to learn and share experience and knowledge[3]. It appears obvious to us that many surgeons have something to say and there is a need to show them how to say it in peer-reviewed journals. We thought this task so important to deserve these precious pages in a leading international surgical journal; we know there are many of you across the world who always wanted to publish but did not know how. We hope the articles will help you get started.

'All you ever wanted to know about [publishing] but never dared to ask' – modified from Woody Allen!

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Full-text electronic version of the *British Journal of Surgery*

Many readers have commented favourably on our initiative using a CD to supply easily accessible archival *BJS* material for all our subscribers. The CD has, however, been costly to produce and sometimes not all that simple to use. Starting in January, the entire *BJS* will be available in an electronic version through our website (www.bjs.co.uk) using a system called *Synergy* set up by our publishers, Blackwell Science. Whole articles may be read or downloaded for printing. There will be links from the references to a Medline database.

The service will be free of charge, at least initially, although users will be required to register and supply a few individual details. The whole of the 1999 *BJS* is already available and issues for 2000 will be added monthly. Further instructions for the best use of *Synergy* and other details about potential future benefits and possibilities will appear in future *BJS* issues. Alternatively, just go to the website at www.bjs.co.uk for further information.

Please let us know your thoughts about these developments as the future of both the electronic and hard-copy versions of the *BJS* are presently under active debate in the Council of the British Journal of Surgery Society.

J. J. Earnshaw
Associate Editor

Committee on Publication Ethics

About the Committee on Publication Ethics (COPE)

COPE was formed in 1997 by a group of biomedical journal editors. They were concerned about the lack of clear guidelines on how to deal with breaches of research and publication ethics; the limited powers available to them to investigate suspected misconduct; and the lack of any independent agency to consider and investigate suspected cases.

COPE provides a regular forum in which editors can advise each other about the management of difficult cases they routinely encounter during their tenure. All cases are dealt with anonymously, the final responsibility remaining with the reporting editor. COPE has no statutory powers and does not make formal recommendations. Nor does it engage in the detection and prosecution of offenders. And it does not deal with complaints from authors.

COPE's remit includes:

Offering advice to editors;
An annual open meeting on issues of relevance to all those involved in the publication of scientific research;
An annual report, the first of which was published last year www.bmj.com/misc/cope;
The formulation of guidelines on good research and publication practice;
Research into the issues;
Considering the need for a national independent agency to deal with research misconduct.

The COPE Report 1999 includes:

The experience of the committee to date;
Proceedings of the open meeting held in April 1999 to set an agenda for good publication practice;
A selection of anonymised cases submitted to COPE for review;
Guidelines on good publication practice.

Guidelines on Good Publication Practice

The Guidelines attempt to define some of the more pertinent issues; advise on how to investigate suspected cases; and suggest how sanctions might be applied to those committing the misdemeanours. They are intended for authors, editors, editorial board members, readers, owners of journals, and publishers.

They specifically address:

Study design and ethical approval;
Data analysis;
Authorship;
Conflicts of interest;
Peer review;
Redundant publication;
Plagiarism;
Duties of editor;
Media relations;
Advertising.

GUIDELINES ON GOOD PUBLICATION PRACTICE

Why the guidelines were developed

COPE was founded in 1997 to address breaches of research and publication ethics. A voluntary body providing a discussion forum and advice for scientific editors, it aims to find practical ways of dealing with the issues, and to develop good practice.

We thought it essential to attempt to define best practice in the ethics of scientific publishing. These guidelines should be useful for authors, editors, editorial board members, readers, owners of journals, and publishers.

Intellectual honesty should be actively encouraged in all medical and scientific courses of study, and used to inform publication ethics and prevent misconduct. It is with that in mind that these guidelines have been produced.

Details of other guidelines on the ethics of research and published codes of conduct are listed in the appendix.

How the guidelines were developed

The guidelines were developed from a preliminary version drafted by individual members of the committee, which was then submitted to extensive consultation. They address: study design and ethical approval, data analysis, authorship, conflict of interests, the peer review process, redundant publication, plagiarism, duties of editors, media relations, advertising, and how to deal with misconduct.

What they aim to do

These guidelines are intended to be advisory rather than prescriptive, and to evolve over time. We hope that they will be disseminated widely, endorsed by editors, and refined by those who use them.

Acknowledgement

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Philip Fulford (Coordinator)
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Other members of COPE
Delegates to the Meeting on April 27 1999
Other corresponding editors

Appendix

The Association of the British Pharmaceutical Industry. *Facilities for non-patient volunteer studies*. London: APBI, 1989.
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Guidelines for phase IV clinical trials, September 1993.
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Other sections of these guidelines will appear in future issues. The full guidelines are available at www.publicationethics.org.uk.

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Clinical dilemma

Crude rates of outcome

Clinical audit using crude rates of outcome uncovers evidence of a substantial difference in survival rates between two hospitals. How should this problem be considered? Steven Julious and Mark Mullee ask: 'How crude are crude rates?'.

Crude rates are a commonly quoted summary statistic used to compare different groups. In education the crude rates of students attaining various grades are used to compare schools. In medicine crude rates are used at different levels, for example region, district, National Health Service Trust, hospital, unit or surgeon[1]. At these different levels, crude rates may be used to compare screening rates, success rates or, as in the present instance, survival rates between different groups. Given that these summary statistics are being used increasingly as a measure of competence, with widespread implications, the question must be asked: 'How crude are these crude rates?'.

The best way to highlight the issues involved is by example. *Table 1* gives the age-specific death rates for black and white residents of the USA[2]. The crude death rate for each group seems to indicate that, at 8·51 per 1000, black Americans enjoy a lower overall crude death rate than white Americans, at 8·95 per 1000, implying that white Americans have a 5 per cent higher death rate. Death rates are often used as a marker for health and wealth, so do these data suggest that black Americans are healthier and wealthier?

When the death rates for each age stratum within each ethnic group are considered, it is evident that for each stratum black Americans have higher death rates than white Americans. As a consequence, if the rates are standardized directly to a standard population (taken as the black and white population combined), the directly standardized rate for black Americans is 12·05 per 1000, compared with 8·86 per 1000 for white Americans. Thus, when corrected for age, the death rate for black Americans is 36 per cent higher than that for white Americans.

The data given in *Table 1* are an example of Simpson's paradox[3]. Simpson's paradox is a situation in which, after allowing for another, possibly confounding, factor, there is a reversal of the effect first observed. In this example, the effect first observed, of black Americans having a lower crude death rate than white Americans, is reversed by adjusting for age. The overall crude death rate is lower for black Americans, despite having higher death rates at each age stratum compared with white Americans, because most deaths occur in the highest age categories; as black Americans die younger, there is less of the population proportionally in these final categories and hence a lower overall rate.

The implication is that, when crude rates are being used, one must question the results of any clinical audit that purports to demonstrate one hospital as superior to another for a given outcome measure. The consequence of such audit findings may be highlighted by analogy with education. A selective school may have better crude pass rates than a non-selective comparator school. However, better exam results do not equate to a better school. If the results were to be broken down by entrance ability of the pupils in the two schools, a situation similar to that highlighted in *Table 1* might be uncovered. Despite this fact, parents are prepared to expend considerable resource to send children to schools perceived to be more 'successful'. Might a similar situation

Table 1 Crude death rates for the resident population of the USA, 1995

	Black population			White population			Standard population (black and white)		
Age group (years)	Deaths (× 10^3)	Population (× 10^3)	Death rate (per 1000)	Deaths (× 10^3)	Population (× 10^3)	Death rate (per 1000)	Deaths (× 10^3)	Population (× 10^3)	Death rate (per 1000)
<1	10·9	621	17·55	21·5	3015	7·13	32·4	3636	8·91
1–14	4·0	8381	0·48	11·1	42713	0·26	15·1	51094	0·30
15–44	50·5	16057	3·15	135·3	97454	1·39	185·8	113511	1·64
45–64	65·5	5362	12·22	300·1	44848	6·69	365·6	50210	7·28
65–74	57·9	1617	35·81	422·8	16644	25·40	480·7	18261	26·32
≥75	93·3	1102	84·66	1060·2	13412	79·05	1153·5	14514	79·47
Total	282·1	33140	8·51	1951·0	218086	8·95	2233·1	251226	8·89

be imagined for 'selective' and 'non-selective' hospitals? Perhaps patients with the worst prognosis tend to gravitate to the most skilled hospital, unit or surgeon, with a consequent distortion of crude results.

What has briefly been highlighted is the problem of comparing any groups by means of crude rates. The simple example in *Table 1* demonstrates that an overall lower crude rate in one group may disguise a true higher rate. If, for example, the performances of two surgeons were being compared, an overall crude rate might favour one surgeon, but this might disguise the fact that he or she operates on lower-risk patients. High-profile incidents, such as the Bristol case, have highlighted the need for clinical performance indicators[4]. The problems associated with the reporting of crude rates and alternative strategies for making comparisons or improving clinical performance have been well reported[5]; with certain provisos, they have a place in clinical audit. However, one concern is not with the issue of falsely high crude rates but with that of falsely low crude rates. If a hospital had a falsely high crude rate, the institution concerned would be likely to offer a quick clarification, but would there be a similar rush to explain a falsely low rate?

In summary, crude rates should be avoided when comparing groups. One must always endeavour to compare like with like by adjusting, where possible, for any factors known to affect the outcome of interest. If such adjustment for known factors is not easy, possibly owing to sparse data, the crude rates should be broken down by any clinical factor of interest. Otherwise, one way for a hospital to improve apparent performance (and resources, if these depend on performance) is not to improve medical skills, but to change the mix of patients treated.

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Review

Imaging of anorectal disease

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Background: Over the past two decades developments in imaging have changed the assessment of patients with anorectal disease.
Methods: The literature on imaging techniques for anorectal diseases was reviewed over the period 1980–1999.
Results: For the staging of primary rectal tumours, phased array magnetic resonance imaging (MRI) may be regarded as the most appropriate single technique. The combination of endosonography or endoluminal MRI with ultrasonography or spiral computed tomography yields similar results. All techniques have limitations both for local staging and in the assessment of distant metastases. MRI or positron emission tomography is preferable for tumour recurrence. For perianal fistula, high-resolution MRI (phased array or endoluminal) is the technique of choice. For constipation, defaecography is the preferred technique, nowadays with emphasis on functional information. The role of magnetic resonance defaecography is currently being evaluated. For faecal incontinence, endosonography and endoluminal MRI give similar results in detecting sphincter defects; endoluminal MRI has the advantage of detecting external sphincter atrophy.
Conclusion: High-resolution MRI, endosonography and defaecography are currently the optimal imaging techniques for anorectal disease.

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Introduction

Imaging is becoming increasingly important in the management of patients with anorectal disease. While barium studies and fistulography were popular previously, over the past two decades numerous new techniques have been introduced for diagnostic assessment. Defaecography, endosonography and magnetic resonance imaging (MRI) have become widely available and have multiple applications. Recent advancements in MRI are high-resolution techniques, dynamic MRI and the introduction of specific contrast media. [^{18}F]fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) visualizes metabolic changes and has been evaluated in patients with rectal cancer. Advances in computed tomography (CT) technology have led to the widespread availability of spiral (helical) CT. The purpose of this review is to discuss these recent developments and to outline the current role of imaging in the management of adult patients with anorectal disease.

Methods

This review is based on a Medline search from January 1980 to January 1999. Keywords used were fistulography, defaecography, proctography, dynamic rectal examination, combinations of endosonography, endoluminal sonography, computed tomography (CT) and magnetic resonance imaging (MRI), anus, anal, rectum, rectal, diseases, fistula(s) and tumor(s)/tumour(s). Additionally, at 1 March 1999 a PubMed search with the keywords incontinence, perianal fistula(s), prolapse, rectal tumor/tumour and anal tumor/tumour was performed for the previous 180 days. From the title and abstracts, relevant literature was selected. Cross-references of the retrieved literature were used to complete the search. Abstract books of recent congresses were checked for relevant abstracts on imaging of anorectal disease.

Tumour

Colorectal cancer in Western countries is a major cause of death; many tumours are located in the rectum[1]. Staging of rectal tumours is performed to select the optimal therapy, as multiple forms and combinations of therapy are available. Such staging should evaluate local tumour extension, and local and distant metastatic disease. Complete evaluation of the colon is also required in all patients as a synchronous colonic lesion occurs in up to 12 per cent[2–4]. For this evaluation colonoscopy is often performed; barium enema may be used as an alternative. Virtual colonoscopy, a new imaging technique based on CT or MRI, has been developed specially for screening high-risk populations for colorectal cancer and accurately detects synchronous lesions[5].

Detection of rectal tumours is by digital examination, sigmoidoscopy and/or barium enema. Depending on the degree of suspicion, many surgeons and gastroenterologists favour sigmoidoscopy because of the additional advantage of histopathological confirmation by biopsy. Barium enema in many institutions is therefore limited to frail patients and for evaluation of the proximal colon for a synchronous lesion. The major role for imaging in staging of rectal tumours is, first, to determine the extent of the tumour in or through the rectal wall, second, to recognize the presence of enlarged lymph nodes or distant metastases and, third, to assess the distance between the distal tumour margin and the anorectal junction.

Local staging: techniques

For local staging CT was used initially, but its limited contrast resolution led to disappointing results[6–9]. Endosonography and MRI have now become the primary imaging techniques. The application of endosonography was a major breakthrough as multiple layers of the rectal wall could be identified, facilitating tumour assessment[10]. Initial reports of MRI were based on the use of a body coil or external surface coils[11–16] that give a large field of view but a moderate signal to noise ratio and so limited spatial resolution. Further development led to the introduction of phased array coil MRI which employs external coils wrapped around the abdomen to give a high signal to noise ratio for a large field of view. Endoluminal coils, initially developed for prostatic MRI, were introduced for imaging of rectal tumours in the early 1990s[17–28]. These coils have the advantage over external coils of high spatial resolution close to the coil, permitting detailed demonstration of the rectal wall and tumour[17–19,25]. A tight stricture or a high stricture prevents optimal use of endosonography and endoluminal MRI as devices cannot be positioned close to the tumour.

Recent research in nuclear medicine has addressed the potential role of FDG-PET[29]. FDG is a glucose analogue used to estimate the local metabolic rate of glucose. In most malignant tumours, including colorectal cancer, glucose utilization is increased and so FDG can be used to recognize the tumour glucose uptake rate.

Local staging: results

There are numerous reports on the T-staging results of endosonography, body coil or surface coil MRI and endoluminal MRI. A few studies have addressed phased array MRI and FDG-PET. Body coil or external surface coil MRI has a reported accuracy of approximately 80 (range 58–95) per cent[12–14,30,31]; a recent study of 28 patients claims an accuracy of 100 per cent[32]. This success is attributed to the combination of dedicated external surface coils, thin slices, a relatively small field of view and optimized slice orientation (slices true axial to the tumour)[32]. An initial report of a T-staging accuracy of 55 per cent for phased array coil MRI was disappointing, but the sequences used were not optimized (thick slices)[33]. More recent studies have suggested a higher accuracy of 75 per cent (*Figs 1* and *2*)[25]. An improvement in results was anticipated from the introduction of endoluminal coils, but this has not been borne out in clinical trials; endoluminal MRI T-staging accuracy is approximately 80 (range 31–89) per cent[19–21,23,27,34,35]. The detailed demonstration of the rectal wall permitted by endoluminal MRI does not result in improved staging accuracy over that of phased array MRI[25,36,37]. It is probable that endosonography is currently the most widely used technique, with a T-staging accuracy of approximately 85 (range 67–93) per cent[38–42].

FDG-PET is said to have a sensitivity of 100 per cent in detecting colorectal carcinoma[16,43–45]. The major drawback of the technique is its low specificity (43 per cent) and limited spatial resolution[16,43–45]. FDG-PET is not therefore the preferred technique for local staging of primary rectal cancer.

The major limitations of all imaging techniques are understaging owing to microscopic invasion and/or overstaging caused by desmoplastic reaction[36,41]. Results are also influenced by previous radiotherapy[46,47]. Few studies have been performed on the assessment of anal sphincter infiltration. Limited data indicate that high-resolution MRI can lead to an accuracy of 88–92 per cent[32,42,48,49].

Comparative studies between imaging techniques are sparse and the number of patients included is relatively small (*Table 1*). To the authors' knowledge no study has been performed comparing all available techniques and neither comparative FDG-PET nor phased array MRI has yet be subjected to any comparative testing. From the comparative data available no single method stands out best, although there is a tendency for higher accuracy with high-resolution techniques. The choice of method will inevitably be influenced by local expertise and availability. Endosonography may be used as staging technique as its accuracy is high and it is relatively widely available. Factors favouring phased array MRI are high-resolution visualization without the need to introduce an intraluminal device and single-test visualization of both tumour and distant metastases.

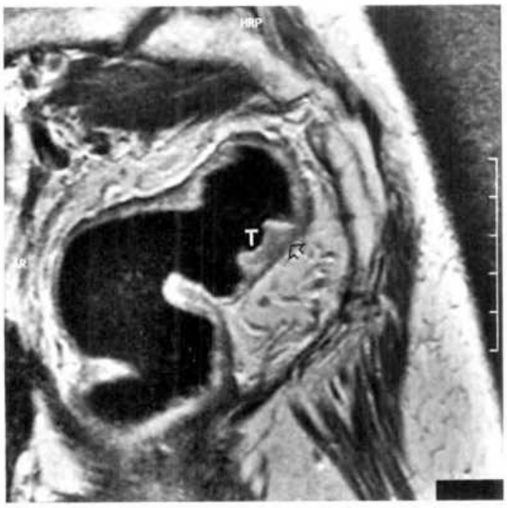

Fig. 1 Phased array magnetic resonance image of a patient with rectal cancer. Sagittal oblique T2-weighted turbo spin-echo reveals a rectal tumour (T) without extension through the wall (open arrow)

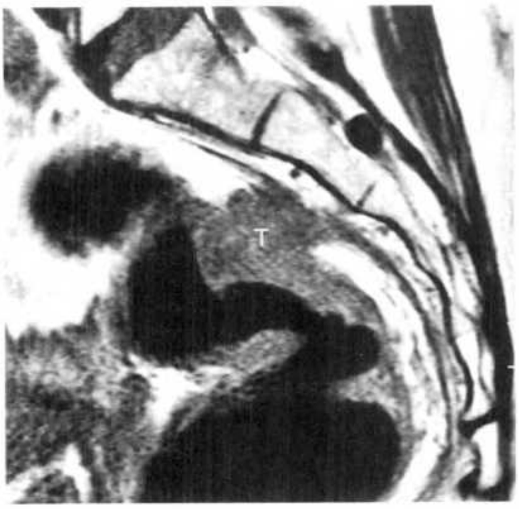

Fig. 2 Phased array magnetic resonance image of a patient with rectal cancer. Sagittal T1-weighted turbo spin-echo demonstrates invasion of the tumour (T) through the rectal wall into the presacral space

Table 1 Rectal tumour T-staging accuracy, reported in studies with surgical and histological confirmation, comparing two or more imaging techniques

			T-staging accuracy (%)		
Reference	Year	No. of patients	Endosonography	Body coil or surface coil MRI	Endoluminal MRI
Waizer *et al.*[7]	1989	13*	85	77	
Thaler *et al.*[15]	1994	37	88	82	
Joosten *et al.*[22]	1995	15†	67	50	78
Starck *et al.*[13]	1995	35	88	66	
Meyenberger *et al.*[36]	1995	6	83		33‡
Hussain[24]	1996	16	82		75
Zagoria *et al.*[26]	1997	10	70		80
Heindel *et al.*[28]	1998	21	76		76

*Results of 13 operated patients in a group of 15; two patients had no surgery. †Total study population 15 patients, all of whom had endosonography; nine had endoluminal magnetic resonance imaging (MRI) combined with double surface coil MRI and six patients had double surface coil MRI only. ‡Including one tumour not reached by the coil

Lymph node staging

Lymph node detection is important for patient management and prognosis[16]. Both endosonography and endoluminal MRI have the limited field of view that is inherent to all endoluminal techniques. Small perirectal lymph nodes are fairly easily detected, but parailiac and para-aortal lymph nodes are missed, necessitating additional imaging. The accuracy of both endosonography[6,10,16,39,50–52] and endoluminal MRI[1[illegible],14,19,23,35,53] for lymph node staging is 70–80 per cent. The specificity of the latter is 50–85 per cent[18,19,21,53]. In a study comparing phased array coil MRI alone with phased array coil MRI combined with an endoluminal coil, the accuracy for local lymph nodes was essentially the same, indicating a preference for phased array coil MRI alone[25].

Lymph nodes are characterized as benign or malignant, predominantly based on the short-axis size of the node[52]. This size criterion is not very accurate and attempts have been made to improve this situation[54,55]. A promising new development is a lymph node-specific MRI contrast medium, ultra-small paramagnetic iron oxide (USPIO). USPIO comprises iron oxide particles that are taken up by benign lymph nodes; preliminary data indicate a high sensitivity (100 per cent) and specificity (80 per cent) for this technique in the identification of lymph nodes with metastatic involvement[56].

An alternative technique is FDG-PET. The specificity of FDG-PET is high (96 per cent), but its sensitivity is low (approximately 30 per cent)[45,57–59]. With FDG-PET lymph node metastases may be detected that are not identified by other imaging techniques.

Liver staging

Liver metastases may be detected by ultrasonography, spiral CT, MRI and FDG-PET[60,61]. Ultrasonography may be used for screening, but it has limitations in the detection of smaller metastases (only 20 per cent of lesions smaller than 1 cm detected) and in the differentiation between haemangioma and metastasis[62]. Increased flow in the hepatic artery, such as can be measured by Doppler sonography or dynamic CT, has been demonstrated to be useful in the detection of occult metastases[63–65].

Currently spiral CT or MRI is often used as the initial or second-line imaging technique. Spiral CT has an overall sensitivity for lesion detection of 81 per cent, with a sensitivity of 91 per cent for lesions greater than 1 cm and 56 per cent for smaller lesions[66]. Recent studies have demonstrated the value of the MRI using the liver-specific contrast medium super paramagnetic iron oxide (SPIO), with accuracies superior to those of spiral CT[60,67,68]. In a study of 51 hepatic resection candidates SPIO-enhanced MRI was significantly more sensitive than spiral CT (81 *versus* 74 per cent)[69].

For surgical patients suspected of having liver metastases, further assessment may comprise CT arterial portography to detect liver lesions less than 1 cm in diameter[60,70]. However, in many institutions CT arterial portography is no longer used as it yields a relatively high number of false-positive findings (13–15 per cent) and is invasive[71,72]. In a comparative study of non-enhanced MRI, SPIO-enhanced MRI and CT during arterial portography, SPIO-enhanced MRI had the highest accuracy (respectively 91, 95 and 93 per cent)[73]. Current assessment often comprises spiral CT or MRI combined with laparoscopic or intraoperative ultrasonography. Both intraoperative ultrasonography and laparoscopic ultrasonography have a high accuracy. The former is more sensitive than SPIO-enhanced MRI (80 *versus* 56 per cent)[68]. The reported sensitivity and specificity of the latter are 100 and 75 per cent respectively[72].

FDG-PET is a valuable tool in the detection of liver metastases of rectal cancer (*Fig. 3*)[29]. In patients with colorectal cancer, FDG-PET has a sensitivity and specificity comparable or superior to those of CT (respectively 88 *versus* 38 per cent and 100 *versus* 97 per cent)[45,58]. However, the CT technique used in these studies (consecutive (non-spiral) 10-mm slices) was not state of the art. In one study FDG-PET was compared with MRI in 18 patients who underwent intraoperative ultrasonography; FDG-PET detected 94 per cent of the lesions and MRI 83 per cent[58]. The MRI technique used was not specified.

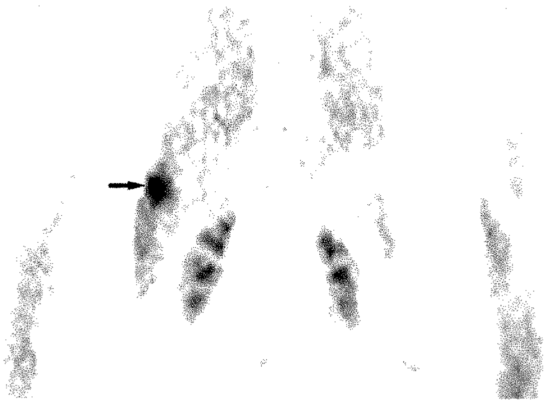

Fig. 3 Male patient with rectal cancer. Coronal [^{18}F]fluoro-2-deoxyglucose positron emission tomography (PET) 60 min after injection reveals a hot spot in the right liver lobe compatible with a liver metastasis, which was proven at histopathological examination. (Courtesy E. F. I. Comans, Department of Nuclear Medicine and PET Centre, Academic Hospital Vrije Universiteit, Amsterdam, The Netherlands)

SPIO-enhanced MRI and FDG-PET are the preferred preoperative imaging techniques for the detection of liver metastases. Spiral CT may be used as an alternative.

Rectal tumour recurrence

Tumour recurrence of rectal cancer can be difficult to differentiate from postoperative scar tissue. CT is not accurate in this context; MRI is superior (68 *versus* 95 per cent)[9,75,76]. Initial reports exploiting the possibilities of MRI focused on signal intensity at T2-weighted sequences and on the morphology of the lesion[77]. Low signal intensity of the mass corresponds with the fibrous tissue of a scar, while a relatively high signal intensity is indicative of tumour. More recent studies have evaluated the use of intravenous contrast medium[78,79]. Older fibrous scar tissue shows little or no enhancement, while the vascular changes in a tumour (e.g. neovascularity) lead to clear enhancement. The best MRI method is probably a combination of these techniques, which can yield an accuracy of 80–85 per cent[80,81].

Some studies have evaluated dynamic enhancement, but its role is not exactly defined[79,82]. Dynamic enhancement is valuable in characterizing recurrent musculoskeletal masses. A steep enhancement of the mass, relating enhancement of the mass to arterial enhancement, indicates tumour recurrence[83]. All criteria are less accurate in the first 1–2 years after treatment. An alternative technique is FDG-PET

(*Fig. 4*)[84,85]. Accuracy has been reported as high as 95–97 per cent, leading to additional diagnostic value over that of CT and MRI[16,57,59,86,87]. Currently FDG-PET or gadolinium-enhanced MRI may be used for the assessment of patients suspected of having recurrent disease. The reported results suggest a preference for FDG-PET over MRI for tumour recurrence, but no comparative study with state of the art techniques exists.

Anal tumours

Results of imaging of anal tumours are very sparse and most studies concern low rectal cancers invading the anal sphincter. Endoluminal MRI is accurate (92 per cent) in determining the presence of anal sphincter invasion[48]. In the personal experience of the authors, involving 16 patients with low rectal cancer, endoluminal MRI was more accurate than endosonography in determining the presence and extent of anal sphincter involvement (88 *versus* 50 per cent)[24]. In one comparative study of endosonography and endoluminal MRI (MRI endoscope) in colorectal tumours, two patients with an anal tumour were included[88]. In these two patients the findings of both techniques were identical (T_2N_0), but no pathological specimens were obtained. The place of phased array MRI has not been determined, but its less detailed demonstration of the anal sphincter muscles may be expected to yield inferior results[37]. In more extensive tumours phased array MRI has the advantage of a large field of view.

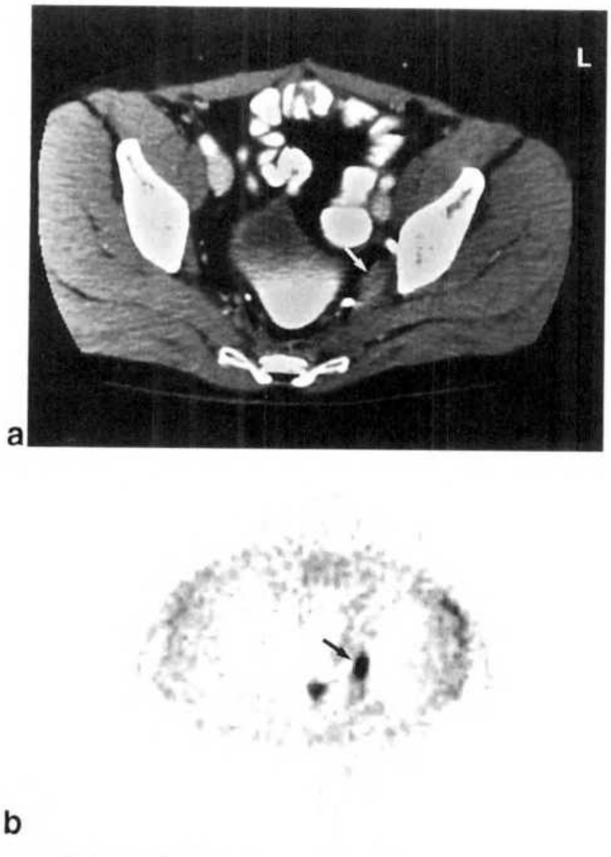

Fig. 4 Patient with recurrent rectal cancer.

a Axial computed tomography (CT) after intravenous contrast medium reveals a mass in the left iliac region (arrow).

b Axial [^{18}F]fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) 60 min after injection reveals a hotspot in the left iliac region (arrow) at the same location as the mass at CT. FDG-PET findings indicate recurrent tumour, as was proven at histopathological examination. The central posterior hotspot is the posterior part of the bladder. (Courtesy E. F. I. Comans, Department of Nuclear Medicine and PET Centre, Academic Hospital Vrije Universiteit, Amsterdam, The Netherlands)

Perianal fistula

Perianal fistulas are caused by cryptoglandular inflammation or Crohn's disease. Clinical history and physical examination will often be sufficient for the diagnosis. The major role of imaging is in establishing the relation of the track to the anal sphincter and related structures. Tracks may be confined to the intersphincteric space and internal sphincter, or may have trans-sphincteric extension from the intersphincteric space through the external sphincter to the ischioanal fossa. Tracks may be complex, with a horseshoe configuration, secondary extensions, extension in the supralevator space or abscesses.

Primary track

Fistulography is an inaccurate technique that in the past decade has been replaced by endoluminal sonography and MRI. Initial endosonographic reports claimed an accuracy of 94 per cent, but these results were not confirmed in further studies (accuracy 50–70 per cent)[89–92]. Major factors contributing to this are the difficult identification of the external sphincter, the difficult differentiation between scar tissue and a track, and the operator dependency of the technique. Modifications such as instillation of hydrogen peroxide in the track or the combination of endoanal sonography with endovaginal sonography may improve track identification (*Fig. 5*)[92–94]. The use of hydrogen peroxide improves accuracy from 62 to 96 per cent[92] but this technique cannot be employed in tracks without an external opening and precautions should be taken to prevent side-effects. In a study of 20 patients, endovaginal sonography added important information to endosonography in four[94].

With MRI the complete sphincter complex, including the external sphincter, and tracks are adequately visualized.

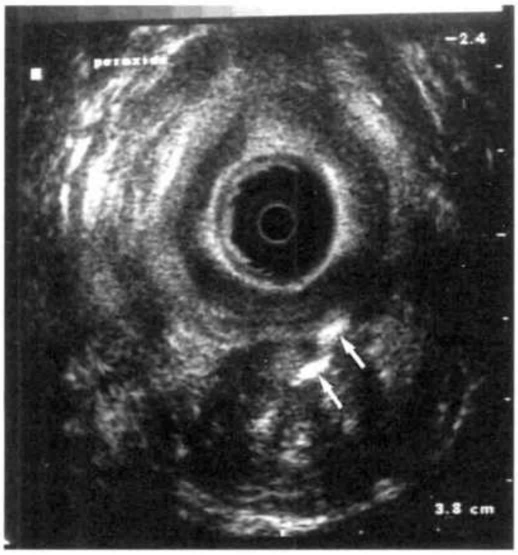

Fig. 5 Endovaginal sonography with hydrogen peroxide in a patient with Crohn's disease reveals an anterior left-sided trans-sphincteric perianal fistula (arrows). (Courtesy A. C. Poen, Department of Gastroenterology, Academic Hospital Vrije Universiteit, Amsterdam, The Netherlands)

MRI was first performed with a body coil or external surface coil with reported accuracies of up to 92 per cent, but later studies have recorded lower values[95–98]. Some advocate the use of saline instillation, which leads to a 20 per cent improvement in accuracy[99]. A disadvantage is that this is a more elaborate procedure that cannot be used in tracks without an external opening. A major advance was the introduction of MRI with high spatial resolution using endoluminal or phased array coils (*Figs 6* and *7*)[98,100–102]. MRI with an endoluminal coil has been demonstrated to be superior to external surface coil MRI in cryptoglandular fistulas (accuracy 86 and 43 per cent)[98]. In a larger series of 30 patients with 18 primary tracks, body coil MRI was superior to endoanal MRI with a surgical concordance for endoanal MRI in 15 tracks and for body coil MRI in 17 tracks[103]. The results of this comparative study are influenced by differences in imaging sequences for both coils as the more sensitive sequence (fat suppression technique) was used only for body coil MRI[103,104]. Furthermore, in this study patients with Crohn's disease were included and endoluminal MRI is not optimal in this disease[105]; tracks may extend outside the limited field of view of an endoluminal coil (*Fig. 7*).

In a comparative study of endosonography and endoluminal MRI in 26 patients with cryptoglandular fistula treated by surgery, endoluminal MRI was more accurate (61 *versus* 89 per cent)[101]. Major differences were the differentiation between scar tissue and an active track, and identification of the external sphincter necessary for

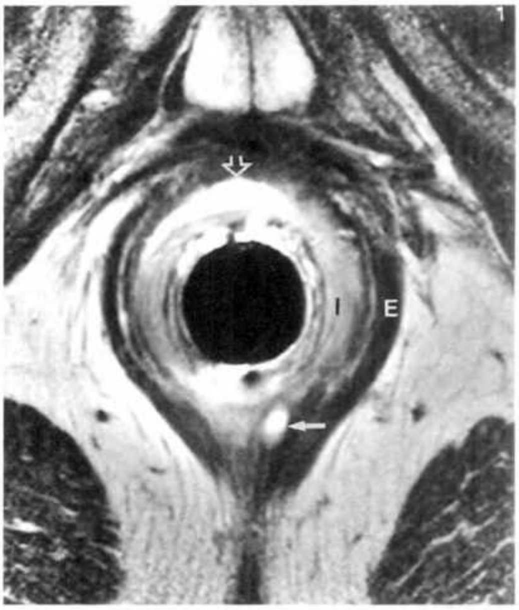

Fig. 6 Endoluminal magnetic resonance image of a patient with a cryptoglandular fistula. Axial T2-weighted turbo spin-echo reveals an anterior intersphincteric track (open arrow) and the intersphincteric course of a left posterolateral trans-sphincteric track (closed arrow). I, internal sphincter; E, external sphincter

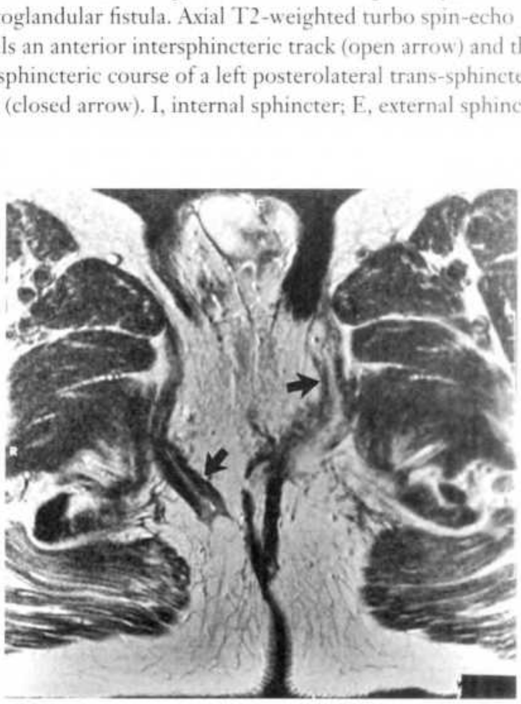

Fig. 7 Phased array magnetic resonance image of a patient with perianal Crohn's disease. Axial T2-weighted turbo spin-echo reveals a track at both sides (arrows) in the ischioanal space and perineal region extending to the adductor muscles

classification. A recent study of 20 patients compared endoluminal MRI and phased array coil MRI with surgery (eight simple fistulas, eight complex fistulas, four no evidence of infection)[106]. Endoluminal MRI was superior to phased array MRI in primary track presence and site (100 *versus* 50 per cent). To the authors' knowledge, no comparative studies between phased array coil MRI and hydrogen peroxide endosonography have been performed. In Crohn's disease tracks may be present or extend outside the sensitive region of endoluminal techniques. Phased array MRI or body coil MRI is therefore preferred in this condition[37,106,107].

Complex fistula

Complex fistulas may have secondary tracks, interconnecting ramifications, a horseshoe configuration or abscesses. Fistulography is very inaccurate. In a series of 25 patients, fistulography was accurate in only four[108]. Endosonography has limitations in detecting secondary extensions, but results improve with hydrogen peroxide-enhanced endosonography (43 *versus* 71 per cent)[90,92]. MRI is more accurate than either digital examination or surgical exploration in secondary track identification[97,109]. In a study of 30 patients, including patients with Crohn's disease, ten secondary extensions were present in eight subjects[103]. Body coil was more accurate as all ten secondary tracks were identified, while with endoluminal MRI only seven tracks within the field of view were identified. A recent study, including eight patients with complex fistulas, compared endoluminal MRI and phased array coil MRI with surgery[106]. Endoluminal MRI was superior to phased array MRI in terms of secondary track presence and site (92 per cent *versus* 54 per cent). The reported results of MRI are superior to those of endosonography, although no direct comparative study has been performed.

Internal opening

Identification of the internal opening is often difficult with endosonography, although hydrogen peroxide may improve the results[90–92]. In a comparison of endosonography and hydrogen peroxide endosonography with physical examination and surgery in 21 patients, both imaging techniques gave poor results[92]. The internal opening was identified with endosonography in one patient, with hydrogen peroxide endosonography in ten, with physical examination in 15 and with surgery in 19. Endoluminal MRI is the optimal imaging technique for internal opening identification. It is superior to endosonography (71 *versus* 43 per cent) and phased array MRI (72 *versus* 61 per cent)[100,101].

Fluid collections

Endoluminal MRI is superior to phased MRI in sphincteric abscess identification and location in both patients with simple tracks (100 *versus* 50 per cent) and complex tracks (93 *versus* 79 per cent)[100]. In a comparative study of endosonography and endoluminal MRI in 28 patients with cryptoglandular fistulas, all abscesses were detected with both techniques[101]. In patients with Crohn's disease, tracks or fluid collections may extend outside the sensitive region of the endoluminal coil, thereby favouring the use of phased array MRI or body coil MRI[103,104,107,110]. In a study of 34 patients, all 21 abscesses were detected by surface coil MRI[105].

Outcome

Surgery may be limited because of concern about postoperative faecal incontinence that may result from extensive operation. MRI can identify tracks in areas not explored at surgery. A recent study has revealed that tracks detected at MRI and not identified at operation proved to be present at follow-up surgery[111]. In this study MRI was a better predictor of outcome than surgery, with positive predictive values and negative predictive values of 73 *versus* 57 per cent and 87 *versus* 64 per cent respectively.

Assessment

MRI is the optimal technique for perianal fistula assessment. For cryptoglandular tracks, endoluminal MRI is preferred for identification of the track and internal opening. As an alternative, phased array MRI or, when not available, body coil MRI may be used. These techniques are easily performed, cause no discomfort (except in claustrophobic patients) and no dedicated coil is necessary. Phased array or body coil MRI should be performed in patients with Crohn's disease. Further refinements of the MRI technique (e.g. optimizing imaging protocols, combination of endoluminal and phased array coils) might improve the results even further.

Anovaginal and rectovaginal fistula

Anovaginal and rectovaginal fistulas may be caused by obstetric trauma, inflammation (e.g. Crohn's disease) or iatrogenic injury (surgery, radiotherapy). Data on imaging are sparse. Anovaginal and rectovaginal fistulas are often collapsed as there is free communication with the vagina. Contrast studies of the vagina or rectum rarely permit the track to be demonstrated and its relationship to the sphincter is not visualized. Such studies have been surpassed by cross-sectional imaging techniques.

Endosonography and endoluminal MRI can demonstrate the track and the anal sphincter. To the authors' knowledge only one comparative study of endoanal/endorectal sonography and endoanal/endorectal MRI has been performed. Sonography and MRI had similar results with a positive predictive value of 100 and 92 per cent respectively[112]. The optimal method has not been established, but high-resolution techniques may be expected to be best as the tracks are short and often collapsed.

Constipation

Constipation has numerous causes and imaging of the anorectum is part of a diagnostic assessment that comprises evaluation of colonic size and configuration, and estimation of colonic transit and faecal evacuation[113]. Plain abdominal radiography may yield information on the presence of faecal impaction. Colonic transit studies with radio-opaque markers may be used to differentiate between slow-transit constipation and obstructed defaecation. Contrast enema may exclude megarectum and Hirschsprung's disease.

For the evaluation of obstructed defaecation, defaecography (also called dynamic rectal examination or evacuation proctography) is performed. The rectum is filled with radio-opaque material and evacuation is imaged during fluoroscopy in a lateral projection, with the patient sitting on a radiolucent commode. The study should be carried out using video recording and spot films of key events. Consecutive 100-mm films give dynamic information but require a considerable radiation dose[114]. If digitization of the fluoroscopic image is available, direct screen measurements of distances or angles are possible when necessary. Further dose reduction may be obtained with pulsed fluoroscopy. Often a vaginal coating will be applied and for an extensive pelvic floor evaluation, for instance for cystocele, the defaecography may be combined with contrast medium in the bladder and small bowel[115–117].

In recent years papers have been published on the use of dynamic MRI in the assessment of patients with constipation and prolapse[118–127]. Most studies report on the evaluation of pelvic floor disorders with dynamic MRI using a conventional magnetic resonance machine. In conventional machines the patient is in a supine position. Some years ago a vertically aligned machine (double doughnut) was introduced for interventional MRI, which also proved valuable for magnetic resonance defaecography in the sitting position[124,125]. Currently the potential of dynamic MRI is being evaluated.

In patients with obstructed defaecation, anismus, intussusception, rectocele and enterocele are frequent findings at defaecography. These defaecographic findings will now be discussed, with emphasis on clinical relevance. Initial studies reported the detection of structural abnormalities[128,129]. More recent research suggests that functional findings should also be taken into consideration and has questioned the relevance of certain structural phenomena (e.g. anorectal angle change, small rectocele).

Anismus

During normal defaecation the pelvic floor and anal sphincter muscles relax and intrarectal pressure rises[130]. Obstructed defaecation may be caused by persistent or paradoxical contraction of the pelvic floor and sphincter muscles during attempts to evacuate[130–132]. Many terms have been used to describe this abnormality (e.g. paradoxical sphincter contraction, spastic pelvic floor syndrome, non-relaxing puborectalis syndrome) but anismus is now the accepted term[133–135]. Initial defaecography studies in patients with anismus described incomplete evacuation, persistent puborectalis impression and, consequently, no increase of the anorectal angle (*Fig. 8*)[133]. However, later studies have reported a wide variation in the value of the anorectal angle in both normal individuals and patients with anismus, as well as variation between observers[135–141]. The anorectal angle is now not considered useful in the diagnosis of anismus. More valuable defaecographic variables for diagnosis are the completeness and duration of defaecation. Evacuation proctography provides a valid estimate of the time and completeness of rectal evacuation[142,143]. The non-physiological filling of the rectum at defaecography does not seem to influence the accuracy of the technique. In a comparative study of defaecography and the rectal balloon expulsion test there was good agreement between inability to evacuate rectal paste and inability to expel a rectal balloon, suggesting that the disordered defaecation was independent of the nature of the rectal content[144]. In a prospective study of 24 patients incomplete evacuation after 30 s was highly suggestive of anismus[145].

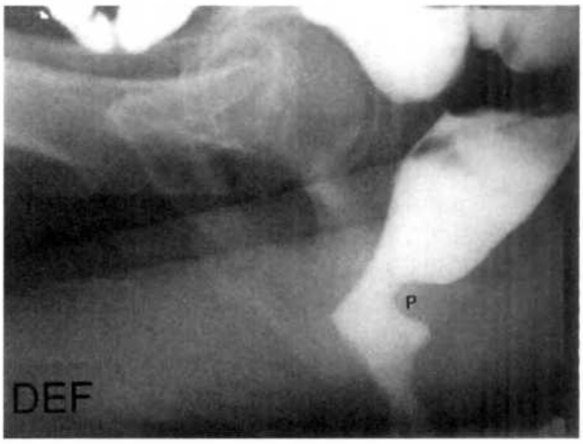

Fig. 8 Dynamic rectal examination (lateral view) reveals a prominent puborectal impression (P) in a patient with anismus

Intussusception

Circular invagination of the proximal rectal wall may occur during defaecation. With downward straining this intussusceptum may remain within the rectum (intrarectal intussusception), occlude the anal canal (intra-anal intussusception) or extend beyond the anal opening (rectal prolapse) (*Fig. 9*). An intussusceptum occupies rectal space and so may cause a sense of incomplete emptying, which may lead to further straining and increase in size of the intussusceptum. Most intussusceptums remain within the rectum or extend to the anal canal. Along with these complete circular invaginations, small mucosal folds may protrude into the proximal rectum. Initially all intussusceptums, including these small mucosal folds, were considered as abnormal findings at defaecography. However, some degree of intussusception might be a normal finding[137,139]. In one study of 47 healthy individuals, 22 had some degree of intussusception[138]. In a further study of 215 consecutive constipated patients[143], 112 had intussusception, which was an isolated finding in 27. These 27 patients had an evacuation pattern similar to that in control subjects except for a somewhat lower initial evacuation rate. Evacuation of the lower half of the rectum is not clearly affected by intussusception, although it may be possible that refilling of the rectum is impaired[143].

The isolated finding of limited intussusception at defaecography is probably not the cause of symptoms; an intussusceptum does not often progress into a more extensive prolapse[146]. Intussusception might be a secondary phenomenon related to some underlying abnormality, which may explain the variation in the results of operation for this condition[147–151]. The frequent association of intussusception with rectocele, enterocele and anismus supports this hypothesis[143,152].

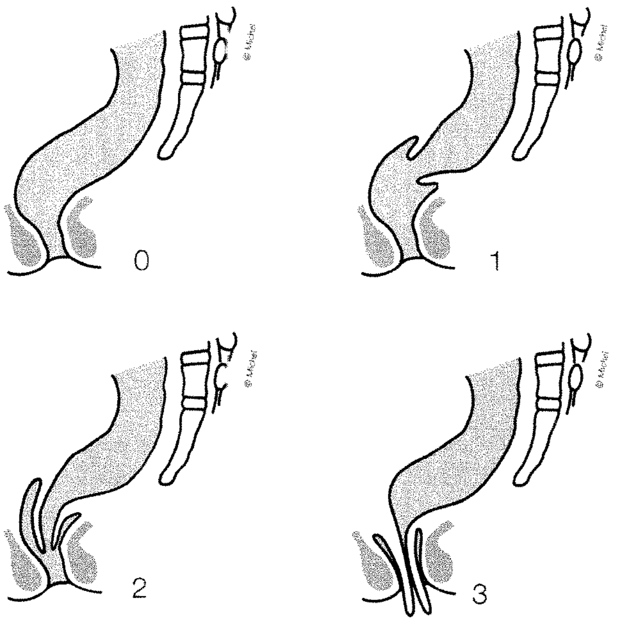

Fig. 9 Grading system for intussusception and rectal prolapse. Grade 0, no intussusception; grade 1, intrarectal intussusception; grade 2, intra-anal intussusception; grade 3, rectal prolapse

Solitary rectal ulcer syndrome is associated with intussusception and complete rectal prolapse[153]. Patients present with rectal bleeding, tenesmus and difficult evacuation. The causative mechanism is probably chronic straining with intussusception and rectal prolapse, leading to trauma and ischaemia of the anterior wall with consequent ulceration[154]. At defaecography an ulcer on the anterior wall may be identified, and often intussusception or rectal prolapse[154,155]. Evacuation is often incomplete and slow[154].

Rectocele

A rectocele is an outward bulge of the (usually anterior) rectal wall. The rectocele herniates through the rectovaginal septum to a site outside the pressure zone created by the raised abdominal pressure[155]. Defaecography and physical examination are of similar usefulness in the detection of anterior rectocele[113]. In a study of 74 women, 73 had a rectocele; six small rectoceles (8 per cent) were not detected at physical examination and three (4 per cent) were not seen at defaecography[113]. A small rectocele is a frequent finding in asymptomatic individuals and often shows no trapping of contrast medium[115,137]. The size of the rectocele does not correlate directly with symptoms[156,157]. Rectoceles may be identified with dynamic MRI[122]. In a comparison of defaecography and dynamic MRI in 44 women with constipation, the latter was more accurate in detecting the 17 rectoceles diagnosed at operation (77 *versus* 86 per cent)[123].

In a study of 47 healthy individuals, 17 of the 21 women had small rectoceles (less than 2 cm) at defaecography[138]. Another study of ten asymptomatic women reported a similar proportion[137]. In a report of 215 consecutive constipated patients[143], 114 had a rectocele larger than 2 cm; in 19 patients this was an isolated finding, with trapped contrast medium in 13. These 19 patients with an isolated rectocele had an evacuation pattern similar to that of control subjects, except for a somewhat lower initial evacuation rate. Larger rectoceles more often demonstrate barium trapping, but this finding may not be related to impaired evacuation[115,156]. The majority of patients with rectoceles have coexisting findings, such as intussusception and anismus[115,143,153]. The presence of a rectocele at defaecography, therefore, may not be related to the symptoms, especially if the rectocele is less than 2 cm in depth.

Enterocele

An enterocele is a herniation of a peritoneal sac along the ventral rectal wall; it is generally filled with small bowel loops (*Figs 10* and *11*). Sometimes the peritoneal sac is filled with sigmoid colon and called a sigmoidocele. Enteroceles often follow hysterectomy or urethropexy, or may be related to chronically increased intra-abdominal pressure[115,158,159]. Enteroceles are difficult to detect by physical examination. In a study including 14 patients with enteroceles, only seven were detected by this means (sensitivity 50 per cent)[115]. Defaecography detected 11 of the 14 (sensitivity 79 per cent), while two of the three enteroceles missed were clearly evident in retrospect as a widening of the rectovaginal space. This probably would have been prevented with the use of small bowel opacification. In another study of 62 women, defaecography was superior to physical examination[117]. At physical examination nine enteroceles were diagnosed, which was correct in three cases and incorrect in three; in the other three the grading was wrong. Enteroceles may be identified with dynamic MRI[122]. In a comparison of defaecography and dynamic MRI in 44 women with constipation, four additional enteroceles (14 *versus* 18 enteroceles) were detected with MRI[123]. An alternative technique is endovaginal sonography, which has an accuracy of 88 per cent[160]. However, the place of this technique is limited, as no more extensive information is obtained than with defaecography.

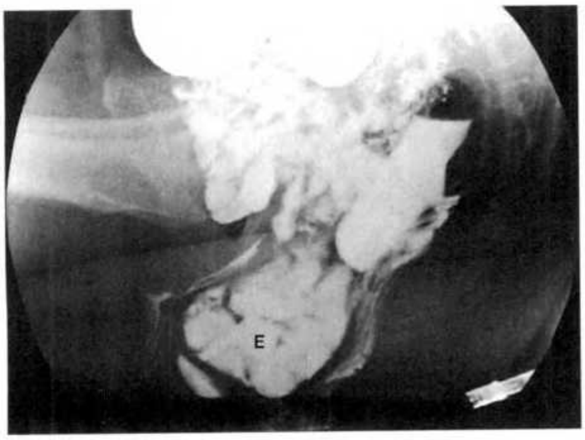

Fig. 10 Dynamic rectal examination (lateral view) reveals a grade 2 enterocele (E)

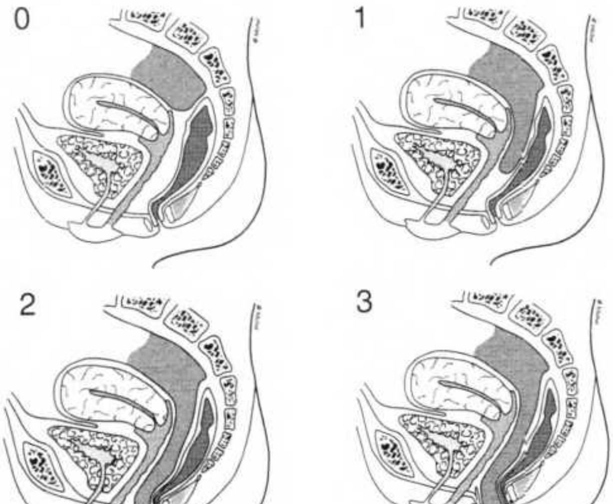

Fig. 11 Grading system for enteroceles. Grade 0, no enterocele; grade 1, enterocele reaching to the distal half of the vagina; grade 2, enterocele reaching to the perineum; grade 3, enterocele protruding out of the anal canal

The technique of defaecography for detecting enteroceles includes vaginal coating and small bowel opacification. To increase the accuracy of both defaecography and dynamic MRI, it is most important to instruct the patient to continue to strain after defaecation. The grading system for enteroceles depends on the extension along the ventral rectal wall[161].

Imaging in constipation is valuable in the differentiation of slow-transit constipation and obstructed defaecation. Defaecography may be used to diagnose anismus, intussusception, rectocele and enterocele as findings related to obstructed defaecation. There is, however, a wide variation of normal defaecographic findings, and such findings (e.g. anismus) may be a secondary phenomenon. These observations have led to the current role of defaecography with evaluation of both anatomical and functional findings, and determination of their relative contributions to obstructed defaecation. Dynamic MRI is probably a valuable alternative to defaecography and may demonstrate abnormalities not revealed by the latter technique; an additional advantage is the lack of ionizing radiation. The scientific evidence is, however, too limited to justify widespread clinical use at this time.

Faecal incontinence

Faecal incontinence is relatively common, especially with increasing age. Some 2 per cent of the population older than 45 years is faecally incontinent. The majority of the affected individuals are women, with childbirth as an important cause. Other causes are diminished rectal compliance, anal surgery, diarrhoea and neurological disease. Initially, neuropathy of the pudendal nerve by stretching of the pelvic floor was thought to be the mechanism causing faecal incontinence after childbirth or chronic straining in patients with constipation[162]. This concept changed after the introduction of endoanal sonography, as direct damage to the anal sphincter muscles proved to be much more common than previously appreciated[163,164]. The majority of patients with so-called neurogenic incontinence have defects of the internal and external sphincters at endoanal sonography[165].

External sphincter

Before the introduction of endoanal sonography the integrity of the external sphincter muscles was often evaluated by physical examination. However, physical examination has been demonstrated to be inaccurate in the detection of anal sphincter defects[166]. Needle electromyography (EMG) is more accurate but its major limitation is the invasiveness of the technique. The pain experienced may prevent the multiple needle insertions necessary for accurate mapping. Endoluminal sonography is as accurate as needle EMG and is painless[167–170]. At endoanal sonography the external sphincter appears as a hyperechoic ring-like structure, poorly delineated within hyperechoic fat. Lesions of the external sphincter are defined as a disturbance of the hyperechoic region outside the hypoechoic internal sphincter. Endoluminal sonography is 90 per cent accurate in detecting anal sphincter defects[167,171–174]. In a study of 44 patients the findings at endoanal sonography were compared with those at operation; all 23 external sphincter defects were demonstrated by the imaging technique[173].

The external sphincter is better visualized with endoanal MRI as there is a large contrast difference between the external sphincter muscle and the surrounding fat. Endoanal MRI has an accuracy of 90–95 per cent in the demonstration of lesions of the external sphincter (*Fig. 12*)[48,175,176]. In a retrospective study of 22 patients with sphincter defects, the findings at endoanal sonography and endoanal MRI were compared with those at operation. MRI was more accurate than endosonography in the detection of external sphincter defects (91 *versus* 73 per cent)[176]. Endoanal sonography has been advocated as an effective technique after operation to evaluate the surgical result[177–179].

Endovaginal sonography and endovaginal MRI are not acceptable alternative techniques as the distance between the transducer/coil and the sphincter is increased and the device is angulated to the axis of the anal canal[180–183]. The use of a more dedicated transducer is suggested to improve results[184]. The value of transperineal sonography is not established as data are lacking[185].

The accurate delineation of the external sphincter with endoanal MRI has led to the possibility of evaluating the muscle mass of the external sphincter[48,175,186–192].

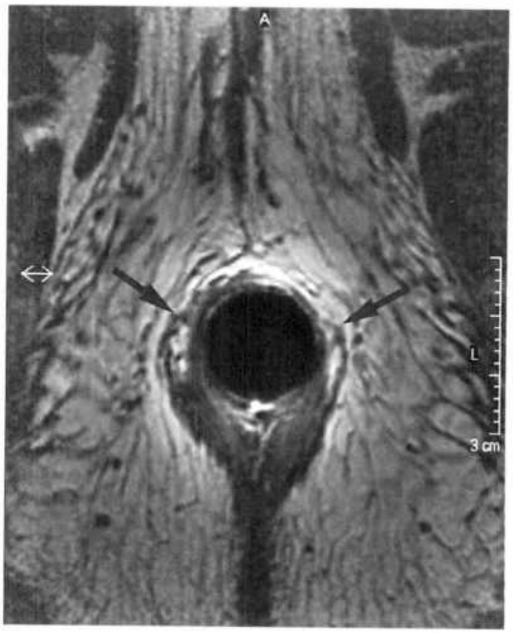

Fig. 12 Endoanal magnetic resonance image of a woman with faecal incontinence. Axial T2-weighted turbo spin-echo reveals an anterior external sphincter defect (arrows). The external sphincter is atrophic (compare with *Fig. 6*)

Sphincter atrophy may occur and endoanal MRI has been proven to be accurate in its demonstration (*Fig. 12*)[193]. This state, detected at endoanal MRI, is a negative predictive factor for the outcome of anterior anal repair. In a comparative study of 20 women, no external sphincter atrophy was detected at endosonography, while the presence of external sphincter atrophy at endoanal MRI correlated with poor outcome after anal repair ($P = 0{\cdot}004$)[194]. Disadvantages of endoanal MRI are increased costs and limited availability.

Internal sphincter

Lesions of the internal sphincter may or may not coincide with external sphincter lesions (e.g. iatrogenic after anal surgery). Internal sphincter lesions may lead to passive incontinence (anal leakage without awareness). Internal sphincter defects may be evaluated by both endosonography and endoluminal MRI. The accuracy of endosonography has been reported as 90–95 per cent, but in a recent comparative study with surgical confirmation endoanal MRI was more accurate than endosonography (77 *versus* 68 per cent)[173,176].

Assessment

Currently, assessment of patients with faecal incontinence comprises endoluminal imaging, manometry and pudendal nerve terminal motor latency (PNTML) measurement. The best endoluminal imaging technique is still debated. Endoanal MRI seems to be the preferred technique, but further study is needed to elucidate its role fully. The advantages of endoanal sonography are availability, limited costs and more widely available experience. The advantages of endoanal MRI are better visualization of the external sphincter and detection of external sphincter atrophy. Manometry is used to determine anal and rectal pressures, as digital examination may be unreliable[195]. Manometric findings indicate the functional contribution of a sphincter defect. PNTML measurement reflects the integrity of the pudendal nerve, and abnormalities indicate neuropathy, which may be concomitant with sphincter defects. The combination of endoluminal imaging, manometry and PNTML measurement gives anatomical and functional information of paramount importance for both management and outcome[196]. The role of defaecography in incontinent patients is limited to those with outlet obstruction symptoms to exclude intra-anal intussusception. In incontinent patients without such symptoms defaecography has little to add to manometry[197].

Conclusion

For staging of primary or recurrent rectal tumours, phased array MRI is the method of choice as this is a single technique for both local staging and evaluation of distant metastases; it is therefore probably the most cost effective method. The use of endoluminal sonography or endoluminal MRI combined with spiral CT or MRI also yields adequate results. FDG-PET imaging may be valuable for recurrent rectal carcinoma. The introduction of lymph node-specific magnetic resonance contrast media and more extensive evaluation of PET will probably further enhance its diagnostic accuracy for rectal cancer staging.

For classification of perianal fistula, phased array MRI is the technique of choice. Endoluminal MRI or hydrogen peroxide-enhanced endosonography may be used as alternative techniques.

Patients with obstructed defaecation should be differentiated from those with slow-transit constipation by means of colonic transit studies. In obstructive defaecation, defaecography should be performed to differentiate between anismus, enterocele and intussusception or a combination of these entities, and for functional information. MRI evaluation of the pelvic floor in constipation might be a further improvement of the technique.

For the assessment of faecal incontinence, both endosonography and endoluminal MRI are accurate techniques; further study is needed to determine which is better. The accurate delineation of external sphincter atrophy is an important advantage of endoanal MRI.

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Review

Acquiring surgical skills

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Background: Technical competence is the bedrock of surgery, yet it has only recently been viewed as a valid area for either critical evaluation or formal teaching.
Methods: This review examines the teaching of surgical skills. The core is derived from a literature search of the Medline computer database.
Results and conclusion: The impetus for surgical change has generally related to the introduction of new technology. Advances initially allowed for open operation within the main body cavities; more recently minimal access surgery has appeared. The latter was introduced in an inappropriate manner, which has led to the evolution of teaching of technical skills away from an apprenticeship-based activity towards more formal skill-based training programmes. There is now a need for a solid theoretical base for the teaching of manual skills that accommodates concepts of surgical competence.

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Introduction

Surgery has a long tradition of passing down skills to apprentices. With time, simple apprenticeships, involving family or friend, gave way to more organized arrangements with formal rules. For example, in Edinburgh during the 16th century, the Master was 'obliged himself to teach and instruct' and had the obligation not to 'transfer his Prentice to another Master'[1]. Such arrangements eventually merged with the residency system.

It is from this historical base that we will approach current efforts aimed at the teaching of manual skills. This will be followed by an outline of how technical skills are learned, an overview of present training programmes, and an account of the methods currently available for teaching and learning surgical skills.

Historical background

At the end of the 19th century the cranium, chest and abdomen were still sanctuaries, only to be entered by the most adventurous[2]. It was only after the introduction of anaesthesia and the promotion of antisepsis that surgery involving the body cavities became practical on a widespread basis, and this era was associated with a shift away from the apprenticeship system towards more formal training (*Table 1*).

William Halsted spent some of his formative years in Germany before returning to the USA, where he established the 'school for safety in surgery', which was characterized by the careful handling of tissues and meticulous attempts at haemostasis[3]. Accompanying this was the importation of the German system of residency training, with its strong emphasis on graded responsibility. A key event was a lecture delivered by Halsted at Yale in 1904 on the training of surgeons[4,5]. The German concept gained support and in 1928 the house of delegates of the American Medical Association approved the principles underlying approved residencies and fellowships[6].

Within the UK the residency system evolved from much deeper traditions. The apprenticeship system promoted the cult of the individual with the emergence of doyens who

Table 1 Comparison between an apprenticeship and participation in a structured programme

Apprenticeship	Structured programme
Art and craft	Science and craft
Long working hours	Shift work
Low technology, low cost	High technology, high cost
See and do	Formal skills training
Problem-driven accountability	Evidence-based accountability
Moderated by peer pressure	Moderated by peer pressure
Mentor evaluation	Objective evaluation
Assessment based upon traits	Competency-based assessment

established 'schools of surgery'. Reputations were promoted through publication. Sir Frederick Treves was one of many who wrote with verve; in 1891 he commented that 'it may be said literally of some intestinal operations, that their success hangs upon a thread'[7]. More than ever before, techniques were being learnt by example rather than by trial and error.

Through most of the 20th century there has been a lack of any systematic approach towards the teaching of basic surgical skills. For example, such matters occupy only the first few pages of the 1972 edition of Farquarson and Rintoul's text[8] on operative surgery, which consists mainly of pithy vignettes. When discussing the tying of knots, the author comments that every time this is done 'two foreign bodies are introduced – the ligature itself and strangulated tissue beyond it'. Another favoured text was written by Arnold K. Henry[9], and this may have been for the writing as much as the content: 'Exposure that will vie effectively with the "great arsenal of chance" must be a match for every shift, and therefore have a range, *extensile*, like the tongue of the chameleon, to reach where it requires'.

A surgical training programme was started in Guy's Hospital, London, in 1972 in 'an attempt to meet the needs of surgical registrars by giving them more security and guidance within a systematic programme leading to consultancy at an early age'[10]. The emphasis was on an adequate range and volume of surgery. In particular, it was appreciated that assisting does not confer the type of knowledge that is required to do an operation. From then until now, surgical training has been seen as a structured and monitored process. However, the formal teaching of manual skills is a recent development.

Reasons for change

The undisciplined introduction of laparoscopic techniques during the early 1990s led Cuschieri[11] to comment about the 'uncontrolled expansion of surgical endoscopic practice which amounted to the biggest un-audited free-for-all in the history of surgery'. In the past, surgical procedures have sometimes been introduced without evaluation and then later abandoned as either useless or frankly dangerous, for example nephropexy for 'floating-kidney', colectomy for epilepsy, ligation of the internal mammary artery for angina pectoris, and prefrontal lobotomy for schizophrenia[12]. However, these historic interventions received much less attention than laparoscopic procedures because they occurred on a different magnitude, in a less demanding era, and were driven by neither the expectations of patients nor commercial interests.

The teaching of operative skills is constrained by the complexity of procedures and medicolegal concerns. Teaching in the operating theatre also takes time and this is in conflict with the need for fiscal restraint and the move towards more civilized hours of work for doctors in training. There is now little opportunity for either reflection or practice during a procedure and this has created the need for formal training outside the operating theatre[13,14].

Another defining factor is an appreciation that the present period of 'open cavity surgery' is finite[15]. We are already witnessing a blurring of the demarcation between the activities of interventional radiologists, physicians who perform clinical procedures, and surgeons. It is becoming evident that those who wish to become surgeons must hold more than the skills that are required for open operation and that the advancing pantechnicon of minimal access surgery will have a profound effect on surgical training. This is consistent with modern organization theory, as espoused by the Drucker Foundation, that it is new technology, rather than politics or social circumstances, that drives change[16].

The acquisition of manual skills is increasingly viewed as a cross-disciplinary exercise. However, it is not always easy to cross professional boundaries. In 1996, Barnes and Ernst[17] compared the opinions of programme directors about vascular surgery training for general surgery residents. Not surprisingly, general surgery programme directors considered that general surgery graduates were fully competent in vascular surgery, should be exposed to more complex vascular surgery during training, and should be granted unlimited vascular surgical privileges on entering practice. The vascular surgery programme directors believed that general surgery graduates lacked competence in vascular surgery, should be exposed to less complex vascular surgery during training, and should have limited vascular surgery privileges in practice.

How surgical skills are learned

The time spent during surgical training should provide the background and personal resources for continuous learning and the acquisition of new areas of expertise[18]. This applies just as much to manual skills as to cognitive and knowledge-based abilities. It is therefore important to have an appreciation of the issues that underpin the attainment of technical competence.

Psychomotor skills

Fleishman and Quaintance[19] have suggested that there are two types of identifiable and measurable motor abilities: perceptual motor abilities and physical proficiency abilities (*Table 2*). Although the general literature contains extensive inventories that detail specific skills, until recently little

Table 2 Types of motor abilities

Perceptual motor abilities	Examples include the coordination of a number of limbs simultaneously, rapidly selecting an appropriate response to an event, aiming precisely at small objects and manipulating objects with speed
Physical proficiency abilities	Examples generally relate to gross physical performance, for instance the ability to coordinate actions while running or to generate bursts of intense muscular effort

work had been performed to identify the perceptual motor abilities that are required during surgery.

Hanna, Cuschieri and co-workers have evaluated a number of motor skills that come into play in laparoscopic surgery. Examples include an ergonomic assessment of the instrument–needle–tissue relationship on efficiency and accuracy of laparoscopic suturing[20], the influence of image display location on aspects of performance such as execution time and knot quality[21], and the effects of reverse alignment displays by the monitor[22]. Such studies should result in a more detailed appreciation of both the taxonomy and components of the psychomotor skills that are employed during surgery.

Hanna *et al.*[23] have also evaluated the ability of right- and left-handed individuals to perform a variety of endoscopic manipulations. They assessed the ability of medical students to negotiate target holes with a probe. Right-handed subjects had a lower error rate when the evaluation involved either the dominant or non-dominant hand, but such differences reflect innate abilities rather than the capacity to improve with training.

Sex influences perceptual and reactive abilities[24]. Women are more proficient than men in finger dexterity and inverted-alphabet printing. On the other hand, men are better at pursuit tracking, repetitive tapping, maze learning and reaction-time tasks. It is thought that some of these differences may result from unequal opportunities and other culturally conditioned influences.

Acquiring motor skills

Dexterity is an important component of psychomotor skills. Manual dexterity has a number of components such as aiming ability, arm–wrist speed and fine finger dexterity. *Table 3* outlines the three stages that occur during the acquisition of a motor skill[25]. The first stage (cognition) is an understanding of the task: individuals who are provided with a clear description and a demonstration of the task are more likely to master a new skill than those who are not. In the second stage (integration), motor skills unique to the task are applied to avoid inefficient movements. In the final stage (automation), the skill becomes automatic so that there is no need to think about each step or rely upon external cues.

Table 3 Stages in the acquisition of motor skills

Phase	Psychomotor element	Focus of instruction
1	Cognition	Perceptual awareness
2	Integration	Comprehension of mechanical principles
3	Automation	Speed, efficiency and precision

The neurological basis for the phase of automation, which underpins technical competence, is the ‘hot-wiring’ of a map of the whole performance into neural circuits. This is why it is sometimes difficult for experts to demonstrate the components of a task to others, for instance the tying of knots. Kirk[26] has pointed out that the skills of an experienced surgeon are not always easy to identify, and complex actions can be learnt at a subconscious level by imitation and may be difficult to break down into component parts. Nevertheless, it is necessary to deconstruct skills so that they can be taught to others.

The kind of formal instruction that best aids the development of motor skills differs between the early and later stages of acquisition. During the initial stages, the most essential factors for learning are perceptual awareness, with an understanding of spatial relations, and a comprehension of the underlying mechanical principles. Later, motor abilities involve speed, efficiency and precision.

As a general principle, repetitive performance of a specific task results in a much better performance of that task than does general training in a variety of skills[27]. This is analogous with problem-solving abilities; the ability to solve specific problems does not have a flow-on effect related to the solving of all problems. It should also be evident that the ability to learn specific manual skills to the point of automation is not indicative of enhanced dexterity. Indeed, it has even been claimed that physicians may be just as dextrous as surgeons[28]. Retention of motor skills appears to be most dependent on the degree to which the skill was perfected, rather than on variables such as the environment. This is a critical point because it implies that many of the basic skills required for surgery can be acquired away from the operating theatre.

The amount of transference of skills between tasks depends on the similarity between the two tasks. This implies that appropriate skills learnt in an inanimate trainer can be carried with advantage into the operating theatre. However, a critical deterrent to securing the transfer of skill is incomplete initial learning of the original task. This raises questions about the value of attendance at an isolated workshop without allowance for the subsequent reinforcement of the relevant skills.

Neuropsychological tests

There is a lack of convincing evidence that neuropsychological tests predict technical competence[29,30]. Schueneman *et al.*[31] tested 120 general surgery residents with a battery of neuropsychological tests and then compared the results with ratings of surgical skills provided by attending surgeons during the course of 1445 operations. Academic predictors, such as the National Board scores and the Medical College Admission Test scores, did not correlate with the surgery ratings, and this was particularly so for complex visuospatial organization, stress tolerance and psychomotor abilities. There is a need to develop neuropsychological tests that are predictive of the ability to acquire surgical skills.

Judgement

Operative skill is a double-edged weapon. As Babcock[32] commented in 1928, 'Brilliantly performed operations may be unnecessary, unwisely selected, or untimed for the particular condition'. Surgical skills require the integration of decision making and mechanical processes. A common criticism of surgical trainees is that 'their hands work faster than their brain does'. Spencer[33] has commented that about 75 per cent of the important events in an operation are related to making decisions and about 25 per cent to manual skill. He has stressed that decision making and dexterity are very different processes. Decision making is a higher intellectual function, whereas manual skills are eye–brain–hand reflexes. Nevertheless, judgement cannot be divorced from technical skill, as evidenced by the concomitant evolutionary development of higher cortical function and dexterity (by reduced thumbs and the ability to carry out precise movements with fingers and opposing thumb).

The learning curve

The concept of a learning curve is useful when applied to surgical skills. It can be applied to experienced surgeons who wish to learn a new procedure as well as to undergraduates and surgical trainees. It is usually constructed in retrospect, rather than being applied as a continuous assessment based on predetermined criteria.

It is possible to estimate the dimensions of a learning curve. For example, experience with laparoscopic cholecystectomy has resulted in changes relating to the operating time, the selection of patients, the conversion rate and the incidence of adverse events[34,35]. Yaegashi *et al.*[36] relied upon operating time and blood loss when suggesting that gynaecology residents need to perform more than 75 hysterectomies to achieve proficiency. In addition, both Meehan and Georgeson[37] and Watson *et al.*[38] have presented evidence that surgeons can become proficient after performing about 25 laparoscopic antireflux procedures. In an ideal world, one would measure and document learning curves for all trainee surgeons.

There is little information available on the relationship between learning styles and surgical decision making, but it is appreciated that there are many different styles of learning: concrete experience, abstract conceptualization, active experimentation and reflective observation[39]. Lynch *et al.*[40] have stressed that clinical performance 'requires additional cognitive skills and abilities, and behaviours that are not adequately reflected in objective measures of academic performance'. It seems that common sense never goes out of fashion.

Current deficiencies in teaching and training

In 1993 the Calman Report[41] promoted the need for standardization in the teaching of basic surgical skills. There were also concerns about trainee surgical staff carrying out unsupervised operations that they had never previously performed. In 1997 Wilson[42] surveyed 276 trainee surgeons and young consultants in the UK. The incidence of first-time unsupervised procedures was alarmingly high in general surgery. Junior trainees (senior house officers) undertook submandibular gland excision, repair of femoral hernia, surgery for testicular torsion, partial gastrectomy, splenectomy and cholecystectomy while their senior colleagues were absent from the hospital. Registrars' unsupervised hepatobiliary procedures included triple bypass for pancreatic carcinoma, common bile duct exploration, laparotomy for liver trauma and a Whipple procedure. As might be expected, many first-time unsupervised procedures are undertaken as out-of-hours emergencies.

Undergraduates

The purpose of undergraduate education is to prepare the student for the practice of medicine. However, a review of doctors in training in New South Wales teaching hospitals found that about one-third considered themselves to be incompetent in technical skills[43]. It is of interest that such comments do not always relate to complex procedures; there has been a failure to instruct students in simple tasks such as gloving and gowning, and the removal of sutures[44]. Ward *et al.*[45] surveyed 205 medical students and trainees in Leicester, UK, and found that the most valued skills were venepuncture, intravenous cannulation and urinary catheterization. *Table 4* lists some examples of the components of a skills programme for undergraduates. There has also been a neglect of manual skills training for doctors during their preregistration period[46–48].

Table 4 Examples of components of an undergraduate skills programme

Behavioural skills	
Theatre etiquette	Gowning and gloving
	Infection control
	Universal precautions
	Teamwork
Patient counselling	Consent
	Breaking bad news
Non-integrated skills	
Instruments	Use of scalpel, scissors, artery forceps
Simple tasks	Removal of sutures
	Application of dressings and bandages
Simple integrated skills	
Surgical tasks	Suturing simple wounds
	Application of plasters
Ward procedures	Venepuncture and intravenous cannulation
	Insertion of nasogastric tube
	Insertion of urethral catheter

General practitioners

Within the UK, the introduction of a contract for general practitioners in 1990 has resulted in an increase in the number of minor surgical procedures performed in general practice[49]. Concerns have been expressed about the level of training that is provided to general practitioners; poor training has been claimed to result in a drop in standards, as monitored by events such as the incomplete excision of skin cancer[50]. In 1997, it was reported that 43 per cent of the general practitioners working in the Scottish Highlands and Western Isles considered that they had inadequate training in minor surgery[51]; of the 86 per cent who wished to attend a training course, more than half believed that it was desirable to have their technical competence assessed by a hospital consultant.

Surgeons

Surgeons have been criticized for not pursuing more vigorous methods of evaluating their clinical practice[52]. It is evident that the credentialing of surgeons for new and innovative procedures is a matter of great concern and that re-skilling in the future may require more than attendance at short courses or 'masterclasses'[53]. There is no agreement about the best way of assessing competence. Indeed, the Executive Director of the American Board of Surgery has commented that the definition of incompetence is elusive[54]. As van der Vleuten[55] has commented, the 'current state of the art in the assessment of professional competence is unfortunately more complex than a recipe book of agreed testing technology options'. Early detection of the 'failed' surgeon still remains a difficult issue.

Teaching surgical skills

The first British skills workshop was held at The Royal College of Surgeons of England in 1977. It was led by David Williams on microsurgery and during the next year Alan Apley held a course on the fixation of fractures[56]. Bevan[57] later held an anastomosis workshop at the Buckston Browne Research Laboratories at Downe, UK, using pig viscera collected fresh from an abattoir. Much has changed since then. The surgical royal colleges in the British Isles have played a key role in formalizing the teaching of surgical skills and have helped to introduce programmes into many countries, including South Africa, Saudi Arabia, Kuwait, Pakistan, India, Zimbabwe, Hong Kong and Australia[58–60].

The current intercollegiate basic surgical skills course is now a mandatory part of surgical training in the British Isles. It consists of 3 days of highly structured laboratory work that includes both formative and summative assessments. It deals with gowning, gloving, draping, knot tying, suturing, basic anastomotic technique, basic orthopaedic techniques and basic endoscopic surgical techniques. This course has proven to be a substantial innovation in basic surgical training.

In the USA, the need for psychomotor skills training in orthopaedic surgery was recognized in the mid-1960s, and in 1975 Lippert *et al.*[61] from the University of Washington School of Medicine held an 18-h course on motor skills for orthopaedic residents. More recently, Reznick's group from Toronto, Canada, has provided a systematic approach to the teaching and assessment of surgical skills. In 1992 it reported on a technical skills programme for first-year residents in general surgery[62]. The programme consisted of introductory didactic sessions and 'wet labs'. The latter included instruction on preparation of the patient and draping, aseptic technique, the principles of bowel anastomosis, incisions, the use and handling of instruments, principles of haemostasis, intraoperative surgical emergencies, surgical assisting and theatre etiquette.

A variety of laboratory-based models has been used to teach basic skills, such as the suturing of skin and the performance of visceral and vascular anastomoses[63–66]. Latex tubing and Penrose drains allow experience in suturing, knot tying and haemostasis. Pigs' feet simulate human skin and have been used for suturing, teaching basic plastic surgical techniques, and exercises in skin incision and the excision of lesions. More complex models relate to aortic aneurysm repair, lung resection, closure of incisions in the abdominal wall, fracture fixation and joint replacement, arthroscopy and simulation of the pelvis for colorectal surgery. A headlamp video camera allows the unobtrusive recording of events, with the videotapes providing a means of assessing progress.

Lossing and Groetzsch[67] performed a controlled trial on the teaching of skills to fourth-year medical students at the University of Toronto. A simulated appendicectomy model was used to teach and test skills related to scrubbing, gowning, gloving, instrument handling (right and left hand), suturing, cutting, use of cautery and stapling. This occurred at both the beginning and the end of the 8-week surgery term and the students were provided with a reference manual. The students in the evaluation arm of the trial had superior skills to those in the control group, who attended another hospital but received the same pre- and post-tests.

Animals

Animal laboratories have the benefit of providing living simulations that mimic operative reality[68]. For example, a canine model has been used to instruct vascular residents in the *in situ* vein bypass technique (a segment of cephalic vein was used to construct a bypass between the brachial and the ulnar arteries)[69]. Improvement in technique is indicated by a decrease in the number of technical complications (missed valves, missed arteriovenous fistulas, poorly constructed anastomoses) and improved patency rate. More recently, young pigs have been used to gain experience in laparoscopic cholecystectomy[70]. The main difficulties with live animal models are moral issues, substantial cost and concern about infectious disease.

A continuing issue is the need to develop substitutes for the use of live animals. Stotter *et al.*[71] have described a model for intestinal anastomoses using γ-irradiated lyophilized porcine or bovine tissues in combination with a purpose-designed holding jig. Because the tissues are sterile, health hazards are avoided and no special laboratory facilities are required. On the basis of considerable experience, Thomas *et al.*[72] have concluded that synthetic tissues can 'provide a useful and functionally reproducible means for learning' basic surgical skills. By way of example, a recent report details a jig simulating the abdominal wall and peritoneal cavity which can be used to teach the techniques of abdominal wound closure and stoma formation[73]. There is now a growing industry involved with the commercial production of such models. The benefits of bench models include lower cost, portability and easy availability.

Minimal access surgery

The learning of laparoscopic surgery does not lend itself to the traditional 'hands-on' apprenticeship model. However, Rosser *et al.*[74] have concluded that basic skills relevant to laparoscopic performance 'can be acquired with a high level of competence in a brief course unrelated to prior surgical experience, sex, or age'. This implies that formal training programmes do have a valid role to play when new technology is being introduced into the surgical community.

The core skills underlying laparoscopic surgery have been identified. Derossis *et al.*[75] from Montreal, Canada, have developed a model to evaluate laparoscopic skills involving a series of structured tasks (peg transfers, pattern cutting, clip and divide, endolooping, mesh placement and fixation, suturing with intracorporeal or extracorporeal knots). The initial laparoscopic cholecystectomy training programme at the University of Maryland in the USA included the use of a jig that enabled the trainee to practise laparoscopic suturing, knot tying and clip application[70].

The skill and the ergonomics of surgeons performing minimal access surgery can be evaluated using set tasks. Hanna *et al.*[76] have established an objective method for assessing the quality of intracorporeal knots based on a study of 2700 such knots. Each knot was evaluated using a tensiometer and a computerized system analysed force–extension curves. A knot-quality score was obtained from the product of the knot-breaking force and the integrated force, expressed as a percentage of the product for the untied ligature. It was found that the breaking force is not a discriminative variable of knot quality and that measuring the breaking force does not reflect the degree of knot tightening. However, the knot-quality score provides a reliable assessment of knot security, and reflects the strength and degree of tightening of the knot.

Simulated operations

Advances in computing, imaging and information transfer have allowed the use of virtual reality in the performance and teaching of surgery[77]. For example, the minimally invasive surgery trainer – virtual reality (MIST-VR) system allows suitable tasks to be performed using standard laparoscopic instruments linked to a computer, which enables the movement of the instruments to be both measured and translated into a graphical display[78]. It is of interest that MIST-VR is based on abstracted graphics so that surgeons are not distracted by the appearance of virtual organs.

Another advance in the acquisition and assessment of manual skills is the Advanced Dundee Endoscopic Psychomotor Tester (ADEPT), which can be used to evaluate clinical competence in endoscopic manipulations[79]. ADEPT was evaluated by having ten senior trainees (specialist registrars) complete 200 structured tasks involving the manipulation of switches and dials using standard endoscopic imaging and surgical instruments[80]. The overall performance on ADEPT correlated well with independent blind assessment of clinical competence. The system is also able to identify innate abilities, for instance aspects of performance that do not improve with practice. Systems such as ADEPT therefore offer the prospect of predicting the maximum level of skill acquisition. Such tests of aptitude may eventually play a role in the selection of trainees.

Computer-assisted learning has the capacity to reduce the need for staff time, but lacks the important ingredient of immediate feedback. Rogers *et al.*[81] found that computer-assisted learning was less effective than a lecture and feedback seminar for teaching medical students how to tie a two-handed square knot. Aspects of Minor Oral Surgery is a highly interactive software program that was commissioned by the Department of Health in the UK as part of the continuing education opportunities for general dental practitioners. The quality of the images of surgical procedures was judged to be a weakness[82].

Teamwork

Teamwork is a neglected component of skills. Attempts to enhance skills performance can be criticized because of the overt concentration on 'singular, unidimensional constructs', that is the mechanical task performed by the surgeon[83]. There is a need to look at other issues, such as sustained attention and the various components of teamwork. One advance, led by anaesthetists and adopted from the airline industry, is the use of simulated operating theatres. It is evident that team dynamics and the attainment of cohesive groups are areas worthy of consideration.

Training the teachers

A 'training the trainers' programme started in the UK in 1994[84]. In a sentinel publication, Peyton[85] has outlined the application of basic educational theory to the teaching of surgical skills. A key feature is an emphasis on the four-stage approach to the teaching of manual skills (*Table 5*). Although this topic has relevance for all surgical educators, further discussion is beyond the scope of this review and interested readers should consult Peyton's book[85].

Table 5 Stages in the teaching of a manual skill as described by Peyton[85]

Phase	Task	Action
1	Demonstration	Instructor demonstrates the skill at normal speed
2	Deconstruction	Instructor demonstrates the skill by breaking it down into simple steps
3	Formulation	Instructor demonstrates the skill while being 'talked through' the steps by the student
4	Performance	Student performs the skill and describes the steps

Assessment

The introduction of a mandatory intercollegiate basic surgical skills course by the surgical royal colleges in the British Isles underlines the need for objective methods of assessment. Although a variety of techniques has been proposed to assess technical skills[86], it is evident that, if the objective is competence-based assessment under realistic conditions, a structured evaluation of performance within the operating theatre is essential. Otherwise one is assessing traits in the absence of either their definition or components. In words that embrace the current jargon, the 'trait' approach to competence has been replaced by the 'person-by-situation interaction paradigm'[87].

Reznick *et al.*[88] from the University of Toronto have applied validity theory to the assessment of technical skill. They point out the inadequacy of comments such as 'a good pair of hands' and stress the need for assessments that are feasible, reliable, relevant and psychometrically sound. They have pursued that goal by developing a programme of objective structured assessment of technical skill[89,90]. Trainees rotate through a number of stations and are assessed performing specific tasks using bench-top simulations, for example abdominal wall closure, control of haemorrhage from the inferior vena cava and tracheostomy. Residents have been assessed using two methods of scoring, task-specific checklists and global rating scales (it appears that global rating is the better method). It has also been concluded that bench model simulation gives equivalent results to the use of live animals. The overall inference is that the objective structured assessment of technical skill programme can assess surgical skills with reliability and validity.

Some studies have concentrated on instrument-related measurements as a form of assessment. Seki *et al.*[91]

Table 6 Steps in the evaluation of a skills exercise

Objectives	Did the participants understand the objectives?
Coverage	Did the course cover the objectives?
Relevance	Will the acquired skills be useful?
Feedback	What did the participants like about the course?
	How could the course be improved?
Changes	What changes should be introduced?

evaluated technical skill in suturing by analysing actual suture tracts; ideal suturing was defined as advancing a needle along its curvature in combination with correct placement. For endoscopic procedures there have been attempts to replace subjective assessments with all-electronic evaluations: distance travelled by instrument tip, number of movements, speed of movement and time.

As early as 1971, Kopta[25] stressed the fact that deficiencies in the teaching and learning of motor skills are unlikely to be corrected unless there is some mechanism to provide reliable and systematic feedback. Such formative assessment, which is used just to provide helpful feedback, contrasts with summative assessment, which is used to award a grade. In addition, feedback from students is an important ingredient when evaluating courses (*Table 6*).

Conclusion

The haphazard introduction of laparoscopic procedures emphasized the need for a more structured approach towards the attainment of technical competence. Such efforts have commenced and seem likely to expand in the future. With the advent of clinical governance, the prospect of revalidation means that the learning of surgical skills and the assessment of clinical competence are now topics in which every practising surgeon has been forced to take an interest.

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Randomized clinical trial

Randomized controlled trial of topical phenylephrine in the treatment of faecal incontinence

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Background: Anal incontinence due to internal sphincter dysfunction is not amenable to simple surgical repair. The α-adrenergic agonist phenylephrine produces contraction of the internal sphincter and raises resting pressure when applied topically in healthy volunteers. The effect of topical phenylephrine in the treatment of faecal incontinence due to internal sphincter dysfunction was investigated.
Methods: Thirty-six patients (22 women) aged 28–81 (mean 58) years with faecal incontinence and ultrasonographically structurally normal anal sphincter muscles were treated with topical 10 per cent phenylephrine and placebo gels, allocated in random order in a double-blind crossover study. Maximum resting anal sphincter pressure and anodermal blood flow were measured. A symptom questionnaire was completed and incontinence score determined using a validated scale.
Results: There were no significant differences in incontinence score, resting anal pressure and anodermal blood flow between the active and placebo treatments. Six patients on active treatment and two on placebo experienced more than 75 per cent subjective improvement. Three patients developed allergic dermatitis to phenylephrine.
Conclusion: This is the first study of the use of a topical pharmacological agent to treat faecal incontinence. This concentration of topical phenylephrine did not produce a significant improvement in symptoms or function. A subgroup of patients may respond. Further studies are required with increased concentrations.

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Introduction

Faecal incontinence affects more than 2 per cent of the adult population[1], the incidence increasing with age and reaching up to 7 per cent in those aged over 65 years[2]. It is a physically and psychologically disabling condition with considerable social stigma such that only one-third of patients ever discuss the problem with a physician and many are unwilling to admit to symptoms or to seek help[3].

The most common cause of faecal incontinence is damage to the anal sphincter during childbirth[4,5], the most important risk factor being forceps delivery[6]. In the absence of such structural injury, isolated degeneration of the internal anal sphincter is the most common cause of faecal soiling[7]. This condition affects both men and women, usually in middle age. There is usually a low resting anal sphincter pressure, and anal endosonography often shows a thin fibrotic internal sphincter.

Significant faecal incontinence resulting from external sphincter injury is often improved substantially by surgical repair. However, internal sphincter injury is not readily amenable to simple surgical repair and functional results are poor[8,9]. Mild to moderate symptoms can often be treated symptomatically using pads, antidiarrhoeal medications such as loperamide, and dietary changes[10,11]. More recently biofeedback training has gained increasing acceptance in the treatment of incontinence from a variety of causes, with results comparable or superior to those obtained with other forms of treatment[12]. However, for many patients these treatments are not successful and complex surgical procedures may not be appropriate for the elderly or medically unfit patient.

A novel option for treatment of faecal incontinence is that of pharmacological agents. The internal sphincter receives sympathetic innervation through both α- and β-adrenergic receptors[13]. α-Adrenergic agonists such as phenylephrine cause contraction of isolated internal sphincter muscle strips *in vitro*[14,15] and increase anal canal pressure *in vivo*[16].

In a pilot study, in healthy volunteers, application of topical phenylephrine gel to the anus resulted in an increase of 33 per cent in maximum resting anal sphincter pressure (MRP)[17]. The optimal concentration was found to be 10 per cent, and the effect was sustained for 6–8 h after a single application. Hence it was concluded that this agent might represent a potential new treatment for passive faecal incontinence resulting from internal sphincter dysfunction. To test this hypothesis a double-blind randomized controlled trial was carried out in patients with faecal incontinence and structurally intact anal sphincters.

Patients and methods

Consecutive patients with passive faecal incontinence referred to the physiology and outpatient departments of a tertiary referral unit were considered for the study. All patients had to have faecal incontinence for solid or liquid stool. Exclusion criteria included pregnancy, ischaemic heart disease, hypertension, aortic aneurysm and treatment with monoamine oxidase inhibitors or tricyclic antidepressants. Patients with underlying treatable causes for incontinence such as inflammatory bowel disease or surgically repairable external sphincter injury were also excluded.

All patients had a clinical examination, which included rigid sigmoidoscopy to exclude inflammatory bowel disease. They were assessed by means of anorectal physiological testing to determine the nature and extent of the functional impairment. This included anal manometry, rectal sensory testing with balloon distension, anal and rectal sensory testing to electrical stimulation, and measurement of pudendal nerve latency to ensure normal sphincter innervation. Endoanal ultrasonography was carried out to determine the structural integrity of the anal sphincters.

Study design

This was a double-blind random-order placebo-controlled crossover study involving two 4-week treatment periods separated by a 1-week washout period. Randomization was carried out by a pharmacist by means of computer-generated random numbers. The randomization code was kept in the hospital pharmacy and made known to the investigators only after analysis of the completed study.

Patients were treated with 10 per cent phenylephrine or placebo cream, with 0·5 ml applied topically to the anus twice daily for 4 weeks. The choice of a 10 per cent concentration and twice-daily regimen was based on previous pilot studies which showed this to be the concentration required to raise the resting anal pressure effectively in volunteers[17]. The placebo and active cream had identical appearance and texture, and were supplied in identical containers.

The degree of incontinence was determined before treatment and at the end of each of the two treatment phases, using a newly validated grading system which was modified from the Wexner scale[10]: worst incontinence was given a value of 24 and no incontinence scored 0[18]. This scale takes into account the frequency of incontinence for solid or liquid stool or gas, alteration in lifestyle, need to wear a pad, urgency and use of constipating drugs. In addition, for each treatment phase, patients were asked to estimate the overall impact of the treatment as a percentage improvement or deterioration of their symptoms compared with symptoms before the trial. Patient psychological profile was assessed before enrolment in the study using the Hospital Anxiety and Depression scale.

Anal manometry and laser Doppler flowmetry were undertaken before the study started and repeated on the last day of each of the two 4-week treatment phases. Informed consent was obtained for the study, which was approved by the local ethics committee.

Statistical analysis

Data were normally distributed and parametric tests were employed throughout. Fisher's exact test was used for categorical data. As there was a difference, of borderline statistical significance, between the two sequence groups at baseline, analysis of covariance was performed for each outcome measure using the baseline value as a covariate. Analysis of variance was performed for percentage subjective improvement. $P < 0{\cdot}05$ was considered statistically significant. Each outcome measure was considered for the treatment effect, a period effect and an interaction between treatment and period effects. It was calculated that a sample size of 16 would allow a difference between means of one standard deviation to be shown at the 95 per cent confidence level and with 80 per cent power for a randomized controlled trial.

Results

Thirty-six patients (22 women) aged 28–81 (mean 58) years were recruited from patients referred to the physiology unit in a tertiary referral centre for assessment of faecal incontinence. The mean(s.d.) duration of symptoms was 5(4) years. Fifteen patients were receiving treatment with loperamide before enrolment into the study. This treatment was allowed to continue throughout the study, as it had not controlled the symptom of faecal incontinence in any patient.

Endoanal ultrasonography allowed selection of patients who had structurally intact internal and external anal sphincter muscles. Any patient with a disruption of either sphincter muscle was excluded from the study.

Eighteen patients received active treatment in period 1 followed by placebo in period 2 (group 1), and the remaining 18 received placebo in period 1 followed by active treatment in period 2 (group 2). The two groups of patients were similar with respect to demographic features, pretreatment psychological profiles and severity of symptoms (*Table 1*). Patients in group 1 had a longer duration of symptoms than those in group 2 ($P = 0{\cdot}02$). Eight patients in group 1 and seven in group 2 were taking loperamide at a constant dose throughout the study.

The results and analysis of data for the crossover study are summarized in *Table 2*. Pretreatment mean(s.d.) incontinence score was 14(4) for all 36 patients. *Figs 1* and *2* show the incontinence scores for each patient at the end of the two study periods. There was some suggestion of a significant interaction between treatment and period for incontinence score ($P = 0{\cdot}1$) and percentage improvement ($P = 0{\cdot}07$), suggesting that the washout period may have been insufficient. There was no significant effect of the treatment on incontinence scores ($P = 0{\cdot}7$) or subjective improvement in symptoms ($P = 0{\cdot}5$). The mean MRP was not significantly different after phenylephrine compared with placebo ($P = 1{\cdot}0$). Similarly, there was no significant difference between phenylephrine and placebo with respect to the anodermal blood flow ($P = 0{\cdot}9$), the latter remaining largely unchanged during either treatment period (*Table 2*). Six patients on active treatment and two on placebo reported more than 75 per cent subjective improvement of their symptoms.

Three patients developed a localized mild dermatitis reaction to phenylephrine consisting of erythema and pruritus. This resolved soon after treatment was discontinued. No other side-effects were reported.

Table 1 Characteristics of patients before treatment

	Group 1 (active–placebo)	Group 2 (placebo–active)	All patients
Age (years)*	57(12)	58(15)	58(13)
Sex ratio (M:F)	8:10	6:12	14:22
Duration of symptoms (years)*	6(5)	3(2)	5(4)
Psychological score*			
Anxiety	6(4)	5(2)	6(3)
Depression	6(5)	4(4)	5(4)
Incontinence score*	15(4)	14(4)	14(4)
MRP (cmH_2O)*	47(20)	62(24)	55(23)

*Values are mean(s.d.). MRP, maximum resting pressure

Table 2 Incontinence score, maximum resting pressure, anodermal blood flow and subjective improvement in symptoms during the two treatment periods

			P‡		
	Group 1 (active–placebo)	Group 2 (placebo–active)	Treatment and period effect	Treatment effect	Period effect
Incontinence score*					
Period 1	12·5(3·4)	12·6(4·2)	0·1	0·7	0·3
Period 2	13·4(4·7)	13·0(4·7)			
MRP (cmH_2O)*					
Period 1	65(21)	54(21)	1·0	0·3	0·6
Period 2	61(18)	55(16)			
Flux*†					
Period 1	196(25)	198(33)	0·9	0·7	0·13
Period 2	204(19)	203(27)			
Improvement in symptoms (%)*					
Period 1	28(38)	9(21)	0·07	0·5	0·9
Period 2	21(31)	14(27)			

*Values are mean(s.d.). †Anodermal blood flow (ml per min per mmHg per 100 ml tissue) MRP, maximum resting pressure. ‡Analysis of covariance

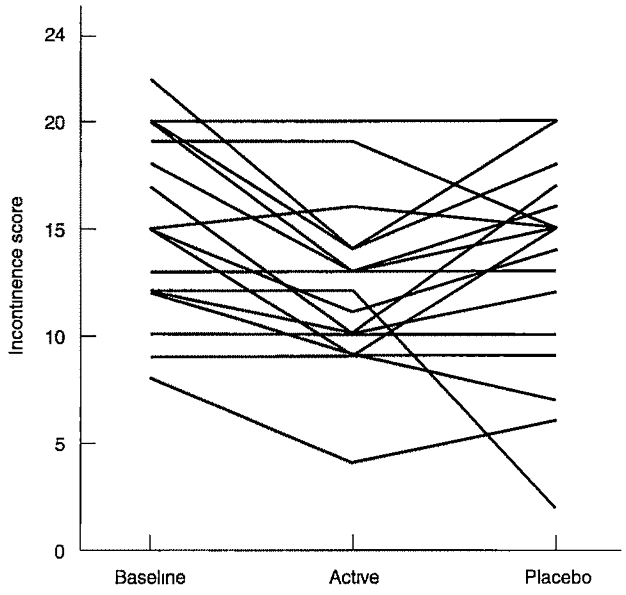

Fig. 1 Incontinence scores for individual patients in group 1 (active treatment in period 1 followed by placebo in period 2)

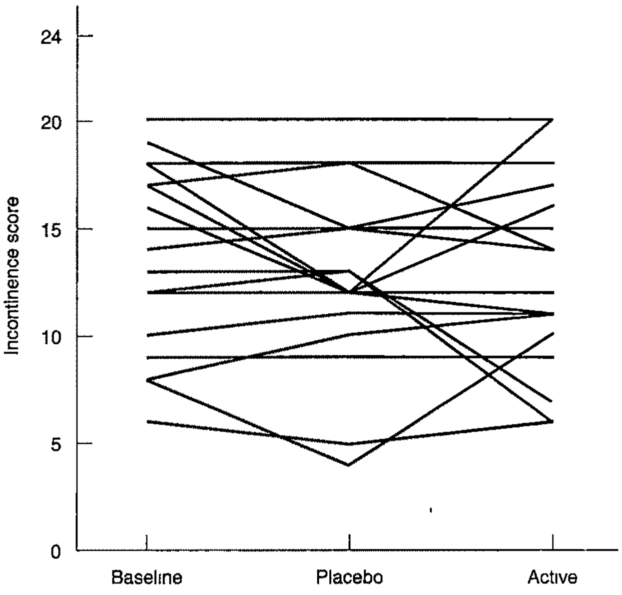

Fig. 2 Incontinence scores for individual patients in group 2 (placebo in period 1 followed by active treatment in period 2)

Discussion

Pharmacological treatment of faecal incontinence is largely limited to the use of oral antidiarrhoeal medication such as loperamide[19]. Loperamide improves stool consistency by reducing its water content, increases the threshold volumes for minimum perception and urgency to defaecate, reduces the sensitivity of the rectoanal inhibitory reflex[20] and decreases motor activity of the large bowel. Although it has been suggested that loperamide may have some effect on anal sphincter tone, this effect appears to be small and is unlikely to account for its beneficial role in incontinence[11].

Patients who were taking loperamide continued to take this drug, without changing the dose, for the duration of the study; loperamide had not relieved the symptom of passive incontinence. A similar proportion of patients was taking the drug in both the active and placebo first phase of the study. For these reasons, together with the fact that the effect of this drug on the anal sphincter is minimal, loperamide was unlikely to have influenced the results of the study.

An alternative pharmacological approach would be to use a topical therapy. Topical phenylephrine is an agent that contracts the internal sphincter smooth muscle, raising resting anal pressure[17]. This study has for the first time used such an agent for the treatment of faecal incontinence due to internal sphincter dysfunction. Previous *in vitro* studies from the authors' laboratory had shown that an α_1 agonist was the most potent means of contracting the smooth muscle internal anal sphincter. This was more effective than an α_2 antagonist.

The results of the study were negative and showed no improvement of symptoms in many of the patients. Six patients did report a greater than 75 per cent subjective improvement in symptoms on the active treatment, as did two patients on placebo. The former six patients had a short duration of symptoms. No statistical comparison was made. Further studies are required to identify patients who may respond to this type of treatment.

The lack of effect of phenylephrine in many of the patients studied may be due to the dosage requirement in patients with incontinence. There is histological and functional evidence that the internal anal sphincter is abnormal in patients with idiopathic faecal incontinence. The *in vitro* responsiveness of the internal anal sphincter to noradrenaline, an important sympathetic neurotransmitter, and to electrical field stimulation, known to stimulate the intrinsic innervation, has been shown to be defective in patients with incontinence compared with controls[21]. The present authors had previously established the dose of phenylephrine required to increase resting anal sphincter pressure effectively in healthy controls[17] and, although this dose may have been adequate for some patients, it appears that a higher dose may be needed for other patients with faecal incontinence.

The aetiology of faecal incontinence in many of the patients in the study was primary sphincter degeneration[7] confirmed by ultrasonography. A further explanation for lack of effect of phenylephrine could therefore be that in primary sphincter degeneration, where there is fibrosis and atrophy of the internal anal sphincter, there is also a reduction in the α-adrenoceptor density and a decrease in the smooth muscle content, rendering the sphincter unresponsive to extrinsic stimulation by topical phenylephrine. The lack of response may be related to the severity of sphincter degeneration in these patients.

A mild localized dermatitis reaction, with erythema and pruritus, was experienced by three patients. This side-effect has previously been reported with use of rectal creams containing phenylephrine[22]. The long-term effects of topical anodermal phenylephrine, if any, are not yet known and remain to be determined in future studies.

In conclusion, although a minority of patients experienced a subjective improvement with active treatment, this concentration of topical phenylephrine did not significantly improve function or symptoms in patients with faecal incontinence. Further investigations using a higher dose or alternative formulation are required.

Acknowledgements

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Original article

Effect of intraportal adoptive immunotherapy on liver metastases after resection of pancreatic cancer

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Background: The prognosis of patients with resected pancreatic cancer remains poor. This study evaluated the effect of adoptive immunotherapy (AIT) using intraportal infusion of lymphokine-activated killer (LAK) cells after curative resection and intraoperative radiation therapy (IORT) on advanced pancreatic cancer.

Methods: Twenty-nine consecutive patients with advanced pancreatic cancer (Japan Pancreas Society stage III or IV) were divided into two groups. The control group ($n = 17$) underwent tumour resection and IORT. The treatment group ($n = 12$) underwent resection, IORT and intraportal infusion of LAK cells combined with recombinant interleukin 2 (rIL-2). The incidence of liver metastasis and the survival rate of these two groups were compared.

Results: Although the overall survival between groups was not statistically different ($P = 0.082$), there were more patients (four) alive 3 years after operation in the test group (36 per cent *versus* zero), and the incidence of liver metastases in the treatment group was significantly lower (three of 12 *versus* ten of 15; $P < 0.05$). LAK therapy influenced survival positively in multivariate analysis.

Conclusion: These preliminary observations suggest that AIT warrants further study as a possible adjuvant for patients undergoing curative resection and IORT for pancreatic cancer.

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Introduction

The prognosis of patients with advanced pancreatic cancer remains unsatisfactory despite recent decreases in morbidity and mortality rates after surgical resection[1]. Some centres suggest that extended resection for patients with advanced pancreatic cancer leads to a better quality of life and longer survival than non-resective conservative therapies[2]. Attempts to improve survival by intraoperative radiation therapy (IORT)[3] and neoadjuvant or adjuvant chemoradiation therapy[4,5] have shown some promise, but no method of preventing liver metastases in this malignancy has been established.

The present study was undertaken to evaluate the effectiveness of intraportal adoptive immunotherapy (AIT) combined with IORT in preventing locoregional recurrence in patients undergoing curative resection for advanced pancreatic cancer.

Patients and methods

From 1989 to 1993, 29 consecutive patients with advanced pancreatic cancer, classified before operation as Japan Pancreas Society (JPS) stage III or stage IV[6] and judged to be resectable technically, were prospectively divided alternately into two groups: a control group (group 1) that underwent tumour resection and IORT, and a treatment group (group 2) that underwent the same surgical management with the addition of AIT with intraportal venous infusion of autologous lymphokine-activated killer (LAK) cells beginning 3 days after operation.

A grossly curative tumour resection combined with IORT (25 Gy) to the tumour bed was performed in all patients. The diagnosis of JPS stage III or IV was made when any of the following staging factors such as tumour size (4 cm or more or 6 cm or more), lymph node metastases beyond regional lymph nodes (N_2 or N_3), definite or severe anterior capsular invasion (S_2 or S_3), definite or severe retroperitoneal invasion (RP_2 or RP_3), or definite or severe portal vein invasion (PV_2 or PV_3) were found. During this period, curative resection was performed for three patients with JPS stage I or II pancreatic cancer. Forty-seven patients diagnosed with JPS stage IV pancreatic cancer were managed by non-resective palliative operations. The resection rate was 43 per cent for pancreatic head cancer and 37 per cent for cancer of the pancreatic body and tail.

Intraoperative factors including blood loss, operating time, type of resection and tumour stage distribution were compared between groups (*Table 1*). In addition, postoperative factors such as length of postoperative hospital stay, operative death and significant morbidity, including intra-abdominal haemorrhage, intra-abdominal abscess, pancreatic or biliary anastomotic leak, or gastric emptying delayed for more than 10 days, were also compared.

The control group (group 1) consisted of 17 patients, 12 men and five women with a mean age of 63 years, and included 11 patients with cancer of the pancreatic head and six with pancreatic body and tail cancer. The LAK-AIT group (group 2) consisted of 12 patients (six men and six women) with a mean age of 62 years, eight of whom had pancreatic head cancer and four pancreatic body and tail cancer. For the patients in group 2, autologous LAK cells mixed with recombinant interleukin 2 (rIL-2) (Shionogi, Osaka, Japan) were administered intraportally via a catheter inserted into the portal vein through the umbilical vein, beginning 3 days after operation. LAK cells were generated from peripheral blood lymphocytes by separation with leucapheresis 3–5 days before operation and culture with rIL-2 1000 units/ml in medium AIM-V (Gibco Laboratories, Grand Island, New York, USA) for 7 days[7]. After 5–7 days of culture, tumour killing activity and contamination were checked. The killing activity of the LAK cells was tested by 4-h ^{51}Cr-release assay using an effector : target ratio of 20 : 1 against natural killer (NK)-sensitive target cells (K562), LAK-sensitive target cells (WISH) or human pancreatic cancer cells (PK-1 and PK-9)[8]. Killing activity was expressed as percentage lysis of target cells according to the formula:

$$\text{Lysis (\%)} = [(E - C)/T] \times 100$$

where E is d.p.m. released into supernatant in the presence of effector cells, C is d.p.m. released by target cells in the absence of effector cells and T is total injected d.p.m. per well.

Table 1 Intraoperative factors of patients undergoing curative resection and intraoperative radiation therapy for pancreatic cancer

	Group 1 (Control) (*n* = 17)	Group 2 (LAK-AIT) (*n* = 12)
Blood loss (ml)*	1340(577)	960(440)
Operating time (h)*	6·5(1·8)	5·5(1·6)
Type of resection		
Pancreatoduodenectomy	11	7
Distal pancreatectomy	5	4
Total pancreatectomy	1	1
Portal vein resection	4	3
Japan Pancreas Society stage		
III	8	9
IV	9	3
UICC stage		
II	3	0†
III	14	4
IV	0	8

*Values are mean(s.d.). LAK-AIT, lymphokine-cell activated killer cell adoptive immunotherapy; UICC, Union Internacional Contra la Cancrum. †$P < 0.05$ *versus* control group (impaired two group test)

LAK cells, free from contamination, which demonstrated high killing activity were suspended in 500 ml 0·9 per cent saline with 5 per cent human albumin. These cells were administered by intraportal venous infusion together with 1×10^6 units rIL-2 over a period of 4 h. After infusion of LAK cells, rIL-2 (1×10^6 units in 500 ml 0·9 per cent saline with 5 per cent albumin) was administered by intraportal venous infusion continuously every 24 h for 3 days. All patients also received 5-fluorouracil (5-FU) 250–500 mg daily by continuous infusion through a central venous catheter for 30 days from day 7 after operation, and thereafter 300 mg daily by mouth.

This study was performed with permission of the ethics committee and the director of Tohoku University Hospital. All patients entered in the study gave written informed consent before the beginning of treatment.

Statistical analysis

The cumulative survival rate was determined by the Kaplan–Meier method for patients who were alive at discharge from hospital. Sites of tumour recurrence were confirmed by autopsy findings and/or by tumour imaging. A log rank test was used to evaluate differences in survival. To compare clinical data at presentation and sites of recurrence, an unpaired two-group test or χ^2 test for independence was used. Data were expressed as mean(s.d.). $P < 0.05$ was considered statistically significant.

Using a Cox proportional hazard model, a multivariate analysis was undertaken to determine which of the factors (LAK-AIT, intraoperative factors, postoperative factors or histological factors) were independent predictors of survival.

Results

Patient groups

Twenty-nine consecutive patients with advanced pancreatic cancer, classified before operation as JPS stage III or stage IV[6] and judged to be resectable technically, were prospectively assigned alternately into the control group (group 1) or the LAK-AIT group (group 2) on referral to this department. The first patient was assigned to group 1 and the study was finished with a patient assigned to group 1. Two consecutive patients were assigned to group 1 by mistake in the middle of the study. When the third patient who was assigned to group 1 died during hospitalization, the fourth patient was again assigned to group 1. Other patients were alternately assigned to the two groups without error. Therefore, 17 patients were assigned prospectively to group 1 and 12 to group 2 before operation.

Intraoperative factors

No differences in blood loss, operating time, type of resection or number of portal vein resections were present between the two groups (*Table 1*). More patients in group 1 were distributed at early Union Internacional Contra la Cancrum stages compared with patients in group 2 ($P<0{\cdot}05$).

Postoperative factors

Two patients in group 1 died in hospital. One patient who underwent total pancreatectomy died from hypoglycaemic shock and another who underwent distal pancreatectomy for pancreatic tail cancer died from toxic shock syndrome. The overall operative mortality rate was 12 per cent (two of 17 patients) for group 1 and zero for group 2. Eight of 17 patients in group 1 and seven of 12 in group 2 suffered complications at operation. Pancreatic anastomotic leak occurred in three of 11 patients who underwent pancreatoduodenectomy in group 1 and in one of seven patients in group 2. Intra-abdominal abscess occurred in three patients in group 1 and in two patients in group 2. Delayed gastric emptying was present in three patients in group 1 and in two in group 2. The postoperative hospital stay was 59 days for group 1 and 70 days for group 2 (P not significant).

In group 2, all patients developed high fever (greater than 38°C) and general malaise during LAK cell infusion and also during rIL-2 infusion, but these symptoms were readily suppressed with antipyretic medication. No severe side-effects or other complications occurred in relation to the immunotherapy. The number of LAK cells administered by intraportal venous infusion varied from 2×10^8 to $1{\cdot}1\times10^{10}$. The NK activity of LAK cells ranged from 20 to 90 (mean(s.d.) 61(23)) per cent, while LAK activity varied from 15 to 81 (44(20)) per cent. Specific killing activity against established pancreatic cancer cell lines varied from 1 to 63 (18(15)) per cent depending on the cell line evaluated.

Histological factors

The incidence of each histological factor in both groups was high and there were no differences between the two groups (*Table 2*).

Liver metastases

Liver metastases occurred before death significantly more often in group 1 than in group 2 (ten of 15 *versus* three of 12 patients; $P<0{\cdot}05$). Local recurrence was also more common in group 1 (14 of 15 *versus* seven of 12; $P<0{\cdot}05$) (*Table 3*).

Survival

Survival rates could be determined for 15 patients in group 1 and 12 in group 2. Survival varied from 3 to 31 months in group 1 and from 4 to 48 months in group 2; all patients, however, died from recurrent cancer. Although overall survival between the groups was not different ($P=0{\cdot}082$) (*Fig. 1*), the 3-year survival rate tended to be greater in group 2 (zero *versus* 36 per cent).

Table 2 Histological factors

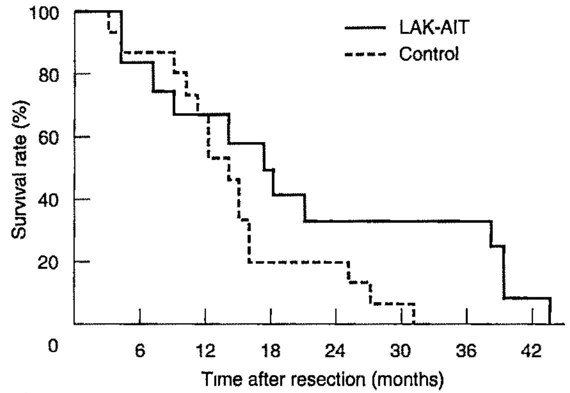
	Group 1 (Control) (n=15)	Group 2 (LAK-AIT) (n=12)
Tumour size ≥3 cm	12	11
Positive resection margins	9	7
Positive lymph nodes	11	12
Differentiation		
Well	5	6
Moderate	8	6
Poor	2	0
Portal vein invasion	4	3
Retroperitoneal invasion	10	12

LAK-AIT, lymphokine-activated killer cell adoptive immunotherapy (impaired two group test)

Table 3 Sites of recurrence

		Site of recurrence				
	n	Liver	Lung	Local	Peritoneum	Bone
Group 1 (Control)	15	10	3	14	7	1
Group 2 (LAK-AIT)	12	3*	2	7*	6	0

Local, pancreas remnant and retroperitoneal space, LAK-AIT, lymphokine-activated killer cell adoptive immunotherapy. $^*P<0{\cdot}05$ *versus* control (χ^2 test)



No at risk

Control	15	13	9	4	3	1	0	0
LAK-AIT	12	10	8	5	4	4	3	1

Fig. 1 Cumulative survival rate after resection and intraoperative radiation therapy for advanced pancreatic cancer. LAK-AIT, lymphokine-activated killer cell adoptive immunotherapy

Multivariate analysis

The probability value and hazard ratio for LAK-AIT in the final multivariate models were 0·04 and 0·97 (95 per cent confidence interval 0·47–1·46) respectively, indicating that LAK-AIT influenced survival positively.

Discussion

The prognosis of patients with advanced pancreatic cancer (stage III or higher) remains poor even after curative resection[1]. Liver metastasis or local recurrence occurs in most patients[9]. Possible explanations for these dismal results involve impairment of immune surveillance in the immediate postoperative period and/or an increased production of cytokines and growth factors which accelerate the growth of microscopic residual regional tumour cells that remain despite radical resection[10,11]. Hence, one oncological strategy in the immediate postoperative period involves immunotherapy designed to prevent residual tumour cell growth.

The effectiveness of AIT using LAK cells and rIL-2 (LAK-AIT) in prolonging survival was limited to patients with melanoma or renal cell carcinoma[12,13]. The effectiveness of LAK-AIT in improving survival after curative resection has been studied previously only in a small number of patients with hepatocellular carcinoma[14]. Similar comparisons of survival between a LAK-AIT group and a control group have rarely been described[15]. This approach using LAK-AIT may be most effective in patients in whom the majority of tumour cells have been resected and who have only a minimal residual tumour burden[16], especially if the therapy can be performed immediately after resection.

Liver metastases after resection of pancreatic cancer are thought to occur either as a result of occult micrometastases that were present before resection or spread of cancer cells to the liver during operative manipulation[17]. The present study was designed to determine the effectiveness of LAK-AIT in preventing liver metastases and improving survival in patients undergoing grossly curative pancreatectomy, IORT and adjuvant treatment with 5-FU, because the number of residual cancer cells, if present, was assumed to be small. The study was based on experimental studies that demonstrated the responsiveness of pancreatic cancer cells to the killing activity of LAK cells *in vitro*[18], and the antitumour effects of LAK-AIT combined with interleukin 2 in human pancreatic cancer orthotransplanted into nude mice[19]. The killing activity of LAK cells in the present study was confirmed by NK activity, LAK activity and pancreatic cancer cell killing activity, and infused LAK cells showed high killing activity in at least one cytotoxicity test. These results suggest that LAK cells generated in culture or those generated in the patients themselves could have at least one type of killing activity *in vivo*.

In a study by Marincola *et al.*[20], LAK cells infused intravenously were delivered to the lung, spleen and liver in nude mice with orthotransplanted human pancreatic cancer. In the present study, intraportal infusion was considered imperative to deliver the LAK cells directly to the liver. The advantage of intraportal administration of LAK cells over intravenous injection has been demonstrated both in a murine model of hepatic metastasis[21] and a clinical study of intraportal or intra-arterial infusion of LAK cells for liver metastasis from malignant melanoma[22]. In addition, the effectiveness of intraportal infusion of interleukin 2 in preventing liver metastasis from colorectal cancer has been reported[23]. The present study suggests that the effect of intraportally infused LAK cells combined with rIL-2 may explain the significantly lower incidence of liver metastasis in the LAK-AIT group compared with the control group. In contrast, the lower incidence of locoregional recurrence in the LAK-AIT group may be explained by the systemic effect of rIL-2.

The overall survival of patients in the LAK-AIT group was no greater than that of those in the control group, probably owing to the small number of patients in the study. Nevertheless, more patients (four) in the LAK-AIT group were alive at the 3-year time point than the control group, suggesting some potential benefit in this subgroup. In addition, multivariate analysis suggested that LAK-AIT may have had a positive effect on survival in patients who underwent tumour resection, IORT and chemotherapy.

No severe side-effects of immunotherapy were observed, and intraportal administration of LAK cells was safely performed only 3 days after major resective operation. Future possible treatment strategies include the use of killer cells that are immunologically more potent and more specific than LAK cells, such as focusing on T cells and advanced gene therapy techniques[24,25]. AIT via intraportal administration might then become an effective postoperative adjuvant therapy against liver metastases of pancreatic cancer.

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Original article

Reliable screening for acute pancreatitis with rapid urine trypsinogen-2 test strip

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Background: This study was designed to evaluate the validity of a new rapid urinary trypsinogen-2 test strip (Actim Pancreatitis) for detection of acute pancreatitis in patients with acute abdominal pain.

Methods: A total of 525 consecutive patients presenting with abdominal pain at two emergency units was included prospectively and tested with the Actim Pancreatitis test strip. Urine trypsinogen-2 concentrations were also determined by a quantitative method. The diagnosis and assessment of severity of acute pancreatitis was based on raised serum and urinary amylase levels, clinical features and findings on dynamic contrast-enhanced computed tomography.

Results: In 45 patients the diagnosis of acute pancreatitis could be established. The Actim Pancreatitis test strip result was positive in 43 of them resulting in a sensitivity of 96 per cent. Thirty-seven false-positive Actim Pancreatitis test strips were obtained in patients with non-pancreatic abdominal pain resulting in a specificity of 92 per cent. Nine patients with severe acute pancreatitis were all detected by the dipstick.

Conclusion: A negative Actim Pancreatitis strip result excludes acute pancreatitis with high probability. Positive results indicate the need for further evaluation, i.e. other enzyme measurements and/or radiological examinations. The test is easy and rapid to perform, unequivocal in its interpretation and can be used in healthcare units lacking laboratory facilities.

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Introduction

Acute pancreatitis is a common abdominal disorder. To date, there is no 'gold standard' for the diagnosis of acute pancreatitis and the diagnosis may be problematic, especially in an emergency setting. The clinical signs of acute pancreatitis, such as upper abdominal pain, epigastric dullness and nausea, are non-specific and may be absent in about 10 per cent of cases[1,2]. Determination of amylase in serum or urine is the principal laboratory method for diagnosing acute pancreatitis[3–5] although it is far from perfect. Hyperamylasaemia may be absent in 19 per cent of cases, so this assay is not sensitive enough as a screening test[6]. The need for more sensitive tests for acute pancreatitis has been pointed out[7]. Presently, contrast-enhanced computed tomography (CT) is the most accurate non-invasive single method of evaluating patients with acute pancreatitis and to assess the severity of the disease[8,9]. However, CT cannot always be performed when acute pancreatitis is suspected because of high costs and limited availability. Thus it too is not suitable as a screening test.

Trypsinogen, which is the inactive precursor of trypsin, is secreted from acinar cells into pancreatic juice. Trypsinogen occurs as two major isoenzymes, trypsinogen-1 (cationic) and trypsinogen-2 (anionic)[10,11]. Premature activation of trypsin within the pancreas is thought to play a crucial role in the pathogenesis of acute pancreatitis[12]. The inflammatory process also leads to leakage of pancreatic enzymes into the circulation, and trypsinogen-2 levels are increased in both serum and urine[11,13]. Trypsinogen-2 and the complex between trypsin-2 and α_1-antitrypsin are therefore accurate diagnostic markers and are of predictive value in assessing the severity of acute pancreatitis[14].

The authors have evaluated a new rapid test strip to detect trypsinogen-2 in urine. The first version of this test strip showed very high diagnostic accuracy in retrospective[13] and prospective[15] studies. The new test strip, Actim Pancreatitis, which is based on new monoclonal antibodies with modified detection limits, is now available commercially (Medix Biochemica, Kauniainen, Finland).

The purpose of the present study was to evaluate prospectively the clinical validity of the novel Actim Pancreatitis test strip in screening for acute pancreatitis by analysing a consecutive series of patients with acute abdominal pain.

Patients and methods

Patients

The prospective study population consisted of 525 consecutive patients admitted to the emergency units at Helsinki University Central Hospital and Helsinki City Hospital between December 1997 and April 1998. All patients presenting with abdominal pain potentially caused by acute pancreatitis were included.

In 45 patients, a diagnosis of acute pancreatitis could be established. The aetiology of acute pancreatitis was alcohol in 32 patients, biliary in seven, drugs in one and unknown in five. There were 16 women and 29 men of mean age 50 (range 30–81) years. In 29 patients the diagnosis was based on consistent clinical findings (epigastric pain, nausea and vomiting) in combination with a raised amylase level (above 300 units/l in serum and/or above 2000 units/l in urine) and diagnostic findings on contrast-enhanced CT or ultrasonography. In 15 patients the diagnosis of acute pancreatitis was based on clinical findings and highly raised amylase levels (serum amylase over 900 units/l, urinary amylase over 6000 units/l). The diagnosis of acute pancreatitis was confirmed by contrast-enhanced CT in one patient without a raised amylase level on admission. In patients with marginally raised amylase levels (300–900 units/l in serum and 2000–6000 units/l in urine) and abdominal pain, pancreatitis was excluded or confirmed with repeated amylase measurements, clinical follow-up and radiological examinations.

The severity of acute pancreatitis was categorized by the clinically based classification of the 1992 Atlanta symposium[16]. Exclusion of acute pancreatitis in 480 patients with acute abdominal disease of extrapancreatic origin was based on clinical, radiographic, endoscopic and surgical findings.

Biochemical measurements

The Actim Pancreatitis test strip is based on the immunochromatography principle. The test was carried out by dipping the tip of the test strip into urine. Trypsinogen-2 in the sample was absorbed and bound to monoclonal antibody-labelled blue latex particles. Then the sample fluid with the latex–antibody–trypsinogen-2 complex migrated across the nitrocellulose membrane with a catching zone containing another antibody specific for a different epitope on trypsinogen-2. The test was considered positive when a clear blue line was detected within 5 min. A control line was used to indicate proper functioning of the strip. If the control line was undetectable the assay was repeated. The detection limit of the test was approximately 50 µg/l.

Urine samples from all patients were obtained in the emergency unit and tested immediately with the urinary dipstick. The concentration of trypsinogen-2 in the samples was also measured by a quantitative immunoenzymometric assay (in-house assay; Medix Biochemica). The samples were stored at – 20°C until the quantitative measurements were performed.

Statistical analysis

Comparison of continuous data was performed with the Mann–Whitney *U* test. Agreement between quantitative trypsinogen-2 concentration and the test strip result was evaluated with the kappa statistic ($\kappa < 0{\cdot}20$ indicates poor agreement and $\kappa > 0{\cdot}81$ very good agreement)[17].

Results

There were 244 women and 281 men, with a mean age of 50 (range 16–90) years. In 45 of the 525 patients with abdominal pain the diagnosis of acute pancreatitis could be established. In 43 of these patients the Actim Pancreatitis test strip showed a positive result, giving a sensitivity of 96 per cent. There were two false-negative results due to relatively low trypsinogen-2 levels (below 50 µg/l) as measured by the quantitative trypsinogen-2 assay. Both patients had a mild attack of acute pancreatitis. The aetiology was alcohol in one and unknown in the other. Thirty-seven of 480 control patients with acute abdominal disease of extrapancreatic origin tested positive (*Fig. 1*). Thus, the specificity of the test strip was 92 per cent. The positive predictive value was 54 per cent and the negative predictive value 99·6 per cent.

The diagnoses of the patients with abdominal pain other than acute pancreatitis, including the 37 false-positive cases, are shown in *Table 1*. Only two of these patients had CT for further diagnostic evaluation, but the diagnoses were achieved by other methods (endoscopy, operation). There were 172 patients with no abdominal diagnosis (*Table 1*), 14 of whom had CT.

Among the 45 patients with acute pancreatitis there were nine with a severe form of the disease. All of these patients showed a positive Actim Pancreatitis test resulting in a sensitivity of 100 per cent. In one patient with severe acute pancreatitis, confirmed by contrast-enhanced CT, the amylase level was not raised whereas the urinary concentra-

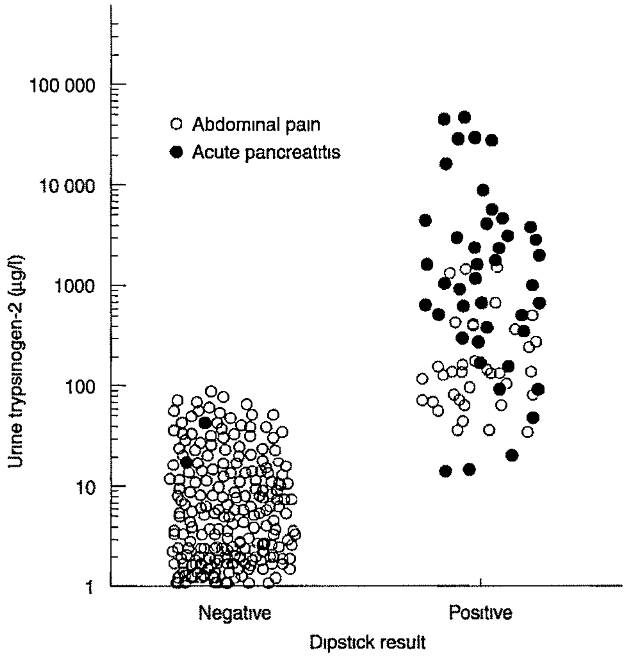

Fig. 1 Results of the urinary trypsinogen-2 dipstick test in relation to quantitative urinary trypsinogen-2 concentration in 45 patients with acute pancreatitis and 480 patients with abdominal pain from other causes

tion of trypsinogen-2 was greatly increased (2330 µg/l) and the test strip result was positive.

The median urinary concentration of trypsinogen-2 in patients with acute pancreatitis was 1030 (range 11·5–48 800) µg/l and in patients with abdominal pain other than acute pancreatitis it was 1·5 (range 0–4500) µg/l. The difference was highly significant ($P < 0{\cdot}0001$, Mann–Whitney U test). The sensitivity and specificity of the quantitative analysis of urinary trypsinogen-2 with a cut-off of 50 µg/l was 91 and 92 per cent respectively. Urinary trypsinogen-2 concentrations were significantly higher in patients with severe acute pancreatitis (median 5640 (range 1010–48 800) µg/l) than in those with mild disease (median 649 (range 11·5–44 300) µg/l) ($P < 0{\cdot}0015$, Mann–Whitney U test). The median urinary concentration of trypsinogen-2 in the nine patients with severe acute pancreatitis was nearly nine times higher than that in patients with a mild course of the disease. In the 37 patients with a false-positive dipstick result, the median urinary trypsinogen-2 concentration was 138 (range 35·5–4500) µg/l. The kappa value was 0·86 indicating very good agreement between the test strip result and the quantitative analysis.

Table 1 Diagnosis in 480 patients with abdominal disorders other than acute pancreatitis

Diagnosis	Total no of patients	No with false-positive results
Acute appendicitis	20	
Acute gastritis or dyspepsia	35	3
Acute gastroenteritis	18	2
Biliary stones	47	1
Blunt trauma	4	
Cardiac disorder or chest pain	11	
Chronic pancreatitis	7	
Colitis	2	
Colonic diverticulosis	14	1
Crohn's disease	1	1
Diabetes with abdominal pain	9	1
Drug or alcohol intoxication	14	4
Duodenal or gastric ulcer	2	
Oesophagitis	6	
Functional disorder of colon	8	
Gastrointestinal bleeding	10	
Hepatic disease	14	4
Hepatorenal syndrome	1	1
Infection	16	5
Intestinal obstruction	11	1
Intestinal perforation	4	3
Malignant extra-abdominal tumour	4	
Malignant abdominal tumour	10	1
Pancreatic pseudocyst	1	
Pulmonary embolus	1	1
Rhabdomyolysis	1	1
Urinary infection, colic or retention	28	1
Other	9	
Unknown	172	6
Total	480	37

Discussion

The Actim Pancreatitis test strip detected patients with acute pancreatitis accurately. The sensitivity (96 per cent) of the new test strip was slightly higher than that of the original test strip (94 per cent) and the specificity a little lower (92 *versus* 95 per cent). The high sensitivity resulted in a very high negative predictive value of more than 99 per cent. Thus, acute pancreatitis could be excluded with a very high probability, which is considered to be of prime importance for a screening test. Another valuable feature was the ability to detect all patients with severe acute pancreatitis. This is to be expected because of the strong correlation between release of trypsinogen-2 and the severity of acute pancreatitis[14]. The probable explanation for the high clinical sensitivity of the test strip is the steep increase in urinary trypsinogen-2 level in acute pancreatitis[14]. Thus the median concentration in patients with pancreatitis was nearly 700-fold that in patients with extrapancreatic abdominal disorders.

False-positive test strip results were obtained in 37 patients with a variety of diagnoses. Thus the positive predictive value was relatively low (54 per cent) indicating that further diagnostic procedures are needed to clarify the cause of a positive result. False-positive results were seen in patients who were seriously ill and therefore needed further diagnostic evaluation and follow-up. In general, the differential diagnosis between acute pancreatitis and patients with false-positive results was relatively simple. The authors recommend that a patient with a positive result undergoes further laboratory evaluation (amylase/lipase) and comprehensive ultrasonography or CT if needed.

In the present study the median urinary concentration of trypsinogen-2 in patients with abdominal pain other than acute pancreatitis was 1·5 µg/l. The detection limit of the urinary test strip (50 µg/l) is approximately 30-fold higher, providing sufficient specificity. The specificity could be somewhat underestimated since subclinical mild acute pancreatitis could not be excluded in all patients with abdominal pain. Raised trypsinogen-2 levels have been reported in hepatobiliary and pancreatic malignancies, in colonic cancer and in chronic pancreatitis[18]. It is likely that the test strip will also detect these conditions.

In general, the correspondence between the test strip result and quantitative analysis of urinary trypsinogen-2 was very good, supporting the use of the trypsinogen-2 test strip. The minor differences between the results of the Actim Pancreatitis test strip and the quantitative urinary trypsinogen-2 assay possibly resulted from the fact that the samples were stored frozen before quantitative analysis; partial activation of trypsinogen-2, leading to degradation, and complex formation between trypsin and its inhibitors may have occurred during storage.

A missed diagnosis of acute pancreatitis leads to inadequate treatment, frequent complications and increased costs. The non-invasive simple urinary screening test evaluated in the present study could be useful in an effort to decrease the number of misdiagnosed cases of acute pancreatitis in an emergency setting.

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Original article

Characteristics of patients with pancreatic cancer expressing a novel cancer cachectic factor

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Background: Recently a novel tumour-derived cachectic factor was identified in the murine MAC16 colonic adenocarcinoma model of cachexia. This factor, provisionally named proteolysis-inducing factor (PIF), was subsequently identified in the urine of weight-losing patients with cancer but not in the urine of weight-stable patients with cancer or weight-losing controls with benign disease. This study determined the nutritional characteristics of patients with pancreatic cancer who excrete PIF in the urine and investigated the relationship between PIF and the acute-phase protein response.

Methods: PIF was isolated from urine by precipitation and ultrafiltration and was then identified by Western blotting of nitrocellulose membranes using a previously developed monoclonal antibody. Full nutritional assessment of patients was undertaken at the same time as urine collection.

Results: PIF was detected in the urine of 80 per cent of patients ($n = 55$). These patients had a significantly greater total weight loss and rate of weight loss than patients whose urine did not contain PIF (median 12·5 (range 4–43) kg *versus* 4·5 (0–14) kg; $P < 0{\cdot}0002$). No association was evident between the presence of PIF in patients' urine and serum C-reactive protein (CRP) concentration. Furthermore, the accelerated weight loss associated with PIF expression also appeared to be independent of the acute-phase response. Overall the presence of PIF was not associated with reduced survival, although the previously reported association between raised CRP concentration and poor prognosis was confirmed.

Conclusion: PIF is associated with an accelerated rate of weight loss in patients with a tumour of the pancreatic head. This observation appears to be independent of the effect of an increased hepatic acute-phase protein response.

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Introduction

Weight loss in patients with advanced cancer is associated with impaired quality of life and reduced survival[1,2]. While the precise mechanisms of weight loss in patients with cancer are often unclear, weight-losing patients with cancer may have substantial disturbances of energy balance. Some patients have a marked reduction of protein-energy intake[3] while others have increased resting energy expenditure[4]. In a proportion of patients these two factors coexist. Energy deficits are greatest in patients who have a raised hepatic acute-phase protein response (APPR) and may indicate that the APPR is a marker of hypermetabolism[3]. Taking into consideration such alterations of energy balance, the calorific value of tissue lost by patients with cancer cachexia frequently exceeds that which might be explained solely in terms of net energy deficit[5]. Furthermore, patients with cancer cachexia may fail to respond to nutritional intervention with hypercaloric protein-energy supplementation[6] (which would theoretically correct all energy imbalances). This observation lends weight to the concept of a metabolic block in the accretion of lean tissue[7] or the action of direct catabolic factors, as does the observation that skeletal muscle protein and subcutaneous fat stores undergo greater depletion than other body compartments, including visceral protein stores[8].

A novel 24-kDa sulphated glycoprotein has recently been identified which appears to mediate weight loss in the mouse MAC16 colonic adenocarcinoma model of cachexia[9]. An identical moiety has also been identified in the urine of weight-losing human patients with pancreatic and other carcinomas[10]. This molecule is recognized by the same monoclonal antibody as the mouse cachectic factor. The murine and human 24-kDa molecules appear to have the same physical characteristics and identical *N*-terminal amino acid sequences. When purified and injected into non-tumour-bearing mice, the human cachectic factor causes weight loss due principally to skeletal muscle proteolysis[11]. The precipitated fraction of urine isolated from healthy subjects and from weight-losing patients with non-malignant disease such as sepsis, trauma, burns and African trypanosomiasis, and from weight-stable patients with cancer, does not contain this cachectic factor and does not induce cachexia when injected into healthy mice[12]. Structural analysis has demonstrated that the glycoprotein contains *N*- and *O*-linked glycosylation sites and that this glycosylation is necessary for functional activity[13]. Thus this factor appears to be a specific proteolysis-inducing glycoprotein which is expressed in weight-losing patients with cancer and has been provisionally named proteolysis-inducing factor (PIF).

The purpose of the present study was to describe the nutritional indices and APPR of a group of patients in relation to expression of PIF.

Patients and methods

Patients

The study group comprised 55 patients with malignant tumours of the head of pancreas. Only patients with histological confirmation of diagnosis were included. Tumour stage was established by a combination of laparoscopy and intraoperative ultrasonography, computed tomography and open operation. Survival was documented from the time of diagnosis and all but four patients died during the course of the study. Two patients were included who had developed recurrence of tumour following previous pancreaticoduodenectomy; in these patients survival was calculated from the time of diagnosis of recurrence. Twenty-four-hour urine collections were obtained from all patients and stored at -20°C without preservative in sterile containers until analysis. No patient had undergone endoscopic stenting, surgery, chemotherapy or radiotherapy in the 4 weeks before collection, and none had evidence of active infection at the time of study. Serum concentrations of the acute-phase reactant C-reactive protein (CRP) were measured by means of an immunoturbidimetric assay (Abbot Laboratories, Maidenhead, UK). Serum albumin concentration was measured with an automated bromocresol green dye-binding technique. Local ethics committee approval was granted for the study and all patients gave informed consent.

Anthropometry

Patients were asked to recall their pre-illness stable weight and duration of weight loss. This was validated where possible from patient records. Patients were weighed on spring balance scales without shoes and wearing light clothing. Height was measured using a wall-mounted stadiometer with the patient standing erect without shoes. Mid-upper arm circumference was measured at the mid-point between the acromion and olecranon processes. Triceps skinfold thickness was measured with Harpenden skin callipers (Holtain, Byberian, UK) and mid-arm muscle circumference was calculated by means of Jelliffe's equation[14].

Body composition analysis

Bioelectrical impedance analysis was performed using a four-terminal multifrequency bioelectrical impedance analyser (Xitron 4000 MFBIA; Xitron Technologies, San Diego, California, USA), operated at a current of 200 μA root mean square. All values were recorded with the subject supine with limbs apart. Total body resistance was recorded at 200 kHz. Values for total body water were obtained using equations validated in a similar patient group[15]. Lean body mass was calculated from total body water assuming a constant hydration coefficient of 0·732.

Resting energy expenditure

Resting energy expenditure was measured by indirect calorimetry using a ventilated hood system (Datex Engstrom, Helsinki, Finland) after an overnight fast in a thermoneutral environment, as described previously[4].

Isolation and detection of proteolysis-inducing factor

Urine (200 ml) was treated with ammonium sulphate (80 per cent w/v) and stirred overnight at 4°C. The precipitated protein product was recovered by centrifugation at 3000*g* for 30 min, dialysed against water through a filtration cell (Amicon, Stonehouse, UK) containing a membrane filter with a molecular weight cut-off of 10 000, and concentrated samples (5 μg) were loaded on sodium dodecylsulphate polyacrylamide gels which consisted of a 5 per cent stacking and a 15 per cent resolving gel. Four immunoblotting gels were transferred to nitrocellulose membranes (Hoefer Scientific Instruments, San Francisco, California, USA), which had been blocked with 5 per cent Marvel (Premier

Beverages, Adbaston, UK) in 0·5 per cent Tween-20 (Sigma, Poole, UK) in phosphate-buffered saline (PBS) at 4°C overnight. The membranes were washed once for 15 min in 0·5 per cent Tween-20 in PBS followed by two more washes for 5 min in Tween–PBS. The membranes were further incubated for 1 h at room temperature in Tween–PBS containing 1·5 per cent Marvel and 10 µg/ml of the specific mouse monoclonal antibody[11] which had been biotinylated using the ECL protein biotinylation module (Amersham, Little Chalfont, UK). After being washed three times as described above, the membranes were incubated for 1 h at room temperature with streptavidin–horseradish peroxidase conjugate (Amersham) at a 1 : 1500-fold dilution followed by three 15-min washes with 0·1 per cent Tween in PBS. Bands were detected with an emission chemiluminescence system (Amersham).

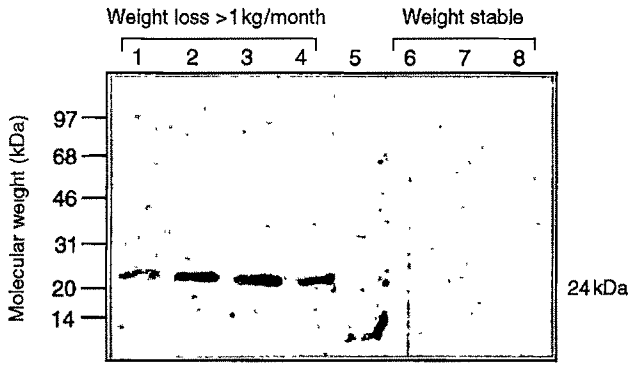


Fig. 1 Representative Western blot for proteolysis-inducing factor (PIF) using an antibody specific to PIF. Lanes 1–4 represent urine samples from patients with weight loss greater than 1 kg/month and show a 24-kDa band, lane 5 represents the molecular weight markers, and lanes 6–8 represent urine samples from weight-stable patients

Statistical analysis

Results are presented as median (range). Comparisons between patients expressing and not expressing the cachectic factor were performed with the Mann–Whitney *U* test. Survival data are presented as cumulative probability of survival (Kaplan–Meier plots) and comparisons between the two groups were performed with the log rank test.

Results

Patient characteristics

The study group comprised 55 patients with malignancy of the head of pancreas. Fifty-three patients had ductal carcinoma of the pancreas, one patient had a periampullary carcinoma and one a cholangiocarcinoma. Using Union

Table 1 Characteristics of patients with pancreatic cancer whose urine was positive or negative for proteolysis-inducing factor

	PIF positive (*n*=44)	PIF negative (*n*=11)	*P*†
Age (years)*	65 (49–86)	70 (56–75)	0.39
Sex ratio (M : F)	31 : 13	7 4	0 73
UICC tumour stage			
2	15	3	0·94
3	6	3	
4	23	5	
Height (cm)*	170 (150–184)	170 (155–183)	0·76
Weight (kg)*	61 (38–90)	62 (46–70)	0·69
Preillness weight (kg)*	76 (45–123)	65 (52–79)	0 009
Weight loss (kg)*	12·5 (4–43)	4 5 (0–14)	0 0002
Preillness lean body mass*	55 6 (32 9–74·8)	47·6 (38·0–57·8)	0 009
Lean body mass*	44·7 (27·8–65·9)	45·4 (33·7–51 2)	0·69
MAMC (cm)*	24 (17–36)	24 (18–26)	0 63
Triceps skinfold thickness (mm)*	9 (4–27)	7 (3–16)	0 27
C-reactive protein (mg/l)*	11 (<10–133)	<10 (<10–42)	0·45
Albumin (g/l)*	38 (20–45)	36 (34–45)	0·9
Resting energy expenditure (kCal per kg body-weight)*	23 8 (16·6–34·0)	23·2 (19 5–27·0)	0 53

*Values are median (range). PIF, proteolysis-inducing factor, UICC, Union Internacional Contra la Cancrum; MAMC, mid-arm muscle circumference. †Mann–Whitney *U* test

Internacional Contra la Cancrum criteria, patients were staged as follows: stage 2, 18; stage 3, nine; stage 4, 28. There were 38 men (69 per cent) and 17 women (31 per cent) of median age 65 (range 49–83) years. Patients had lost a median of 12 (range 0–43) kg (pre-illness body-weight 74 (45–123) kg *versus* weight at diagnosis 61 (38–90) kg; $P < 0{\cdot}0002$). This resulted in a significant fall in median (range) body mass index (25 (18–31) pre-illness *versus* 21 (15–28) at diagnosis; $P < 0{\cdot}001$).

Detection of proteolysis-inducing factor

Western blotting identified 44 patients who expressed PIF and 11 who did not express this factor in their urine; a representative Western blot is shown in *Fig. 1*. The characteristics of patients who did and did not express PIF are given in *Table 1*. There were no significant differences between patients whose urine contained the factor and those whose urine did not with respect to age, sex or tumour stage at the time of study.

Weight loss

Patients whose urine was positive for PIF had a greater pre-illness stable weight and had experienced significantly greater weight loss compared with those not expressing the factor (*Table 1*). The duration of weight loss was similar in the two groups, although the rate of weight loss was significantly greater in patients expressing PIF than in those who did not (2·8 (0·5–10) *versus* 1·0 (0–3·1) kg/month respectively; $P < 0{\cdot}0001$) (*Fig. 2*). There was no association between the rate of weight loss and stage of disease.

Anthropometry

No significant differences were observed in relation to arm anthropometry or total body water between patients whose urine contained PIF and those whose urine did not (*Table 1*).

Biochemical factors

No significant differences in either serum CRP or albumin concentrations were observed between patients expressing PIF and those who did not (*Table 1*). Rate of weight loss was greatest in patients whose urine contained PIF irrespective of the serum CRP concentration (*Fig. 3*). There was no correlation between serum bilirubin concentration and either CRP or PIF expression.

Survival

All but four patients died during the course of the study. No significant survival difference was observed dependent on

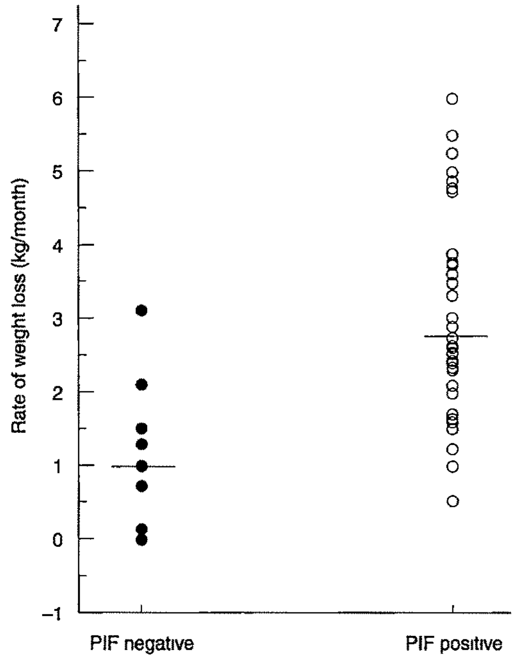


Fig. 2 Rate of weight loss in patients with pancreatic cancer whose urine did or did not contain proteolysis-inducing factor (PIF). Bar denotes median value

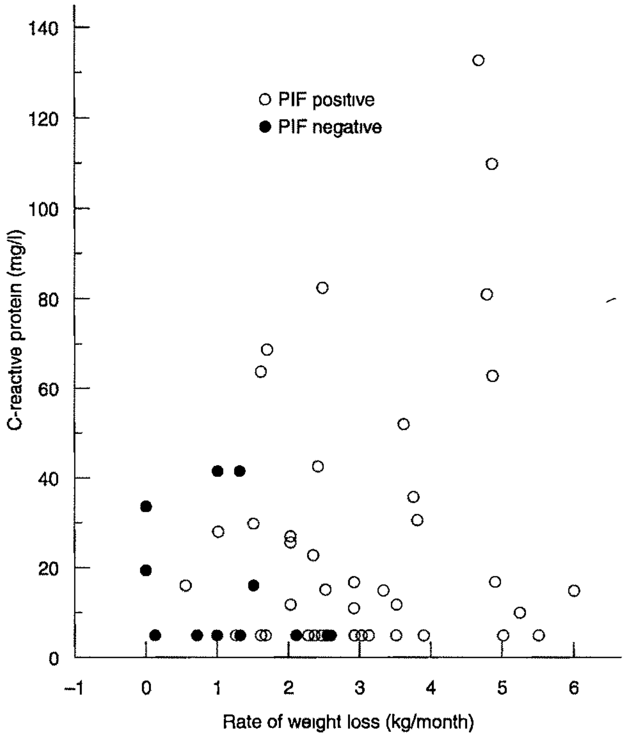
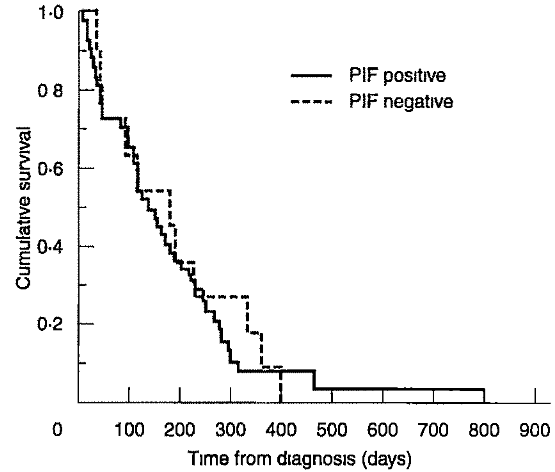
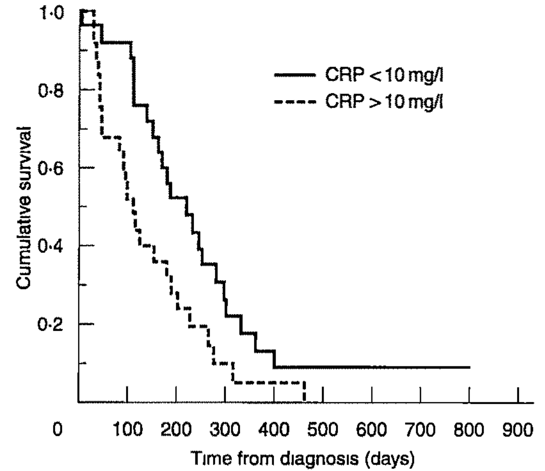


Fig. 3 Rate of weight loss of patients in relation to serum C-reactive protein concentration. PIF, proteolysis-inducing factor



No at risk						
PIF positive	11	7	4	2	1	0
PIF negative	44	29	16	5	3	1

Fig. 4 Cumulative probability of survival in patients with pancreatic cancer whose urine contained or did not contain proteolysis-inducing factor (PIF)



No. at risk						
CRP < 10 mg/l	25	23	13	6	3	1
CRP > 10 mg/l	30	13	7	2	1	

Fig. 5 Cumulative probability of survival in patients with pancreatic cancer whose serum C-reactive protein (CRP) concentration was greater or less than 10 mg/l. $P < 0\cdot05$ (log rank test)

the detection of PIF in the urine (*Fig. 4*). Survival duration was, however, significantly greater in patients with a CRP level of less than 10 mg/l compared with that in those with a raised serum CRP concentration ($\chi^2 = 3\cdot9$, 1 d.f., $P < 0\cdot05$) (*Fig. 5*). Survival was also greater in patients with a serum albumin concentration of 35 g/l or more compared with that in those with a low serum albumin concentration ($\chi^2 = 8\cdot8$, 1 d.f., $P < 0\cdot004$).

Discussion

In the MAC16 murine colonic adenocarcinoma model, animals are thought to lose weight due to the direct effects of proteolytic and lipolytic factors. Some animals with delayed weight loss were found to have antibodies that recognized a 24-kDa factor which co-purified with a lipid mobilizing factor[9]. Subsequently a mouse monoclonal antibody directed against the 24-kDa factor was produced by hybridoma fusion. The factor has a novel *N*-terminal amino acid sequence (YDPEAASAPGSGNP) and is capable of inducing protein degradation in isolated gastrocnemius muscle preparations; it has been named PIF[11,12]. The monoclonal antibody directed against PIF was also found to recognize a 24-kDa moiety in the urine of weight-losing patients with cancer[10]. In the present study 55 patients with tumours of the head of the pancreas were studied. The sample population had a similar pattern of weight loss to that described previously[16]. Using Western blot analysis, PIF was identified in the urine of 44 of 55 patients. These patients had a significantly greater total weight loss and rate of weight loss than patients in whom the factor was not identified. In a previous study it was shown that PIF is not detectable in the urine of patients with benign weight-losing disease states[10]. This supports the concept that PIF is a cancer-specific cachectic factor. In the present study no correlation was identified between expression of PIF and anatomical stage of disease. This may indicate that expression is determined by the phenotype of the tumour rather than by bulk of disease. A longitudinal study might be useful to ascertain whether patients in whom PIF is undetectable at the time of diagnosis produce the glycoprotein later in the natural history of their illness.

Since PIF isolated from the urine of patients with cancer can induce proteolysis of skeletal muscle when injected into animals, it would seem logical to assume that evidence of proteolysis may also be manifest in patients whose urine contained PIF. In the present study, however, no differences were identified with respect to arm muscle anthropometry between patients whose urine contained PIF and those whose urine did not. This may represent sample error since the median preillness body-weight of patients whose urine contained the factor was significantly greater than that of patients who did not. The consequence of this is that, although patients whose urine was positive for the factor had experienced a greater total weight loss at the time of study, there was no difference in body-weight between the two groups. Another possibility is that production of PIF is in some way related to body mass. The present study has not provided objective evidence that PIF induces muscle proteolysis in humans. A longitudinal study using more sophisticated techniques would be required to ascertain whether PIF expression is associated with clinically detectable muscle proteolysis.

No association was evident between PIF status and survival or between weight loss and survival. Serum CRP concentration correlated inversely with survival duration, and serum albumin concentration correlated with survival duration, which concurs with previously reported data on CRP and albumin as indicators of poor prognosis[17]. Previous studies have indicated that the acute-phase protein response is persistently raised in approximately 50 per cent of patients with pancreatic cancer and is associated with reduced protein-energy intake, increased basal metabolic rate and increased rate of weight loss. In the present study there was no significant difference in CRP concentration in patients who expressed PIF compared with those who did not. PIF expression appeared to be associated with a high rate of weight loss and this relationship appeared to be independent of CRP concentration.

These data confirm that patients whose urine contains PIF, antigenically identical to the proteolytic factor associated with cachexia in the MAC16 colonic cancer model, experience greater weight loss than patients whose urine does not contain this factor. From the present study the source of weight loss could not be identified reliably. Further research is required into the regulation and production of PIF and its precise mechanism of action.

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Original article

Experimental study of the effects of deletion variant of hepatocyte growth factor on hepatic ischaemia–reperfusion injury

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Background: Hepatic ischaemia–reperfusion (IR) injury is still a serious complication following liver surgery. The effect of the deletion variant of hepatocyte growth factor (dHGF) on hepatic IR injury was examined in rats.

Methods: Male Wistar rats were divided into two groups after 90 min of partial liver ischaemia: the dHGF group which was given dHGF 0·5 mg/kg intravenously immediately after reperfusion, followed by 0·5 mg/kg every 12 h, and the control group, which received vehicle buffer only. Serum chemistry, histopathological findings and liver weights were compared between the groups.

Results: In the dHGF group, the increase in serum alanine transaminase and hyaluronic acid levels was significantly reduced, and the serum albumin level increased after reperfusion. The extent of hepatic necrosis 24 h after reperfusion was decreased in the dHGF group. Moreover, the proportion of terminal deoxynucleotidyl transferase-mediated 2′-deoxyuridine 5′-triphosphate nick end labelling-positive hepatocytes 6 h after reperfusion was reduced in the dHGF group. The non-ischaemic-, ischaemic- and whole-liver weight : body-weight ratio significantly increased in the dHGF group after reperfusion. The proportion of proliferating cell nuclear antigen-positive hepatocytes in the dHGF group markedly increased after 6 h after reperfusion in the non-ischaemic lobes, while in the ischaemic lobes it increased 24 h after reperfusion.

Conclusion: These data suggest that dHGF not only improves recovery from IR injury, but also accelerates recovery from these injuries. dHGF may be an effective pharmacological agent for prevention and treatment of hepatic IR injury.

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Introduction

Ischaemia–reperfusion (IR) injury of the liver frequently occurs during liver surgery[1–4]. Hepatic hilar vascular occlusion during hepatic resection, used to minimize intraoperative blood loss, hypotension or cardiac arrest before graft perfusion in liver transplantation, renders the liver seriously anoxic[5,6]. In such situations, IR induces reactive oxygen species and chemical mediators that enhance the functional impairment of the liver[1–6].

Hepatocyte growth factor (HGF) is a kringle-containing polypeptide growth factor and is a ligand for the *c-met* proto-oncogene product[6,7]. HGF is a multifunctional cytokine and promotes mitogenesis, motogenesis and morphogenesis in a variety of cells[6,7]. Moreover, HGF has been proven to have hepatocyte protective effects in the setting of various liver injury models[6–13]. The deletion variant of HGF (dHGF) is a splice variant of HGF, which is purified from human embryonic lung diploid fibroblasts, and lacks five amino acids of HGF[12,13]; dHGF has more mitogenic property towards hepatocytes than HGF[12,13].

Most efforts to prevent hepatic IR injury have focused on suppression of immunological and inflammatory events. Attempts to protect the targeted liver itself have not been studied extensively. The aim of this study was to investigate whether dHGF elicits a protective effect towards hepatic cells, improves liver function and enhances hepatocyte regeneration after hepatic IR injury in rats.

Materials and methods

Experimental design

Seventy-two male Wistar rats (Institute of Experimental Animals, Kyushu University, Fukuoka, Japan) weighing 110–150 g were used. The rats were allowed free access to water and standard laboratory food, and were kept under controlled environmental conditions with a 12-h light and dark cycle. Before operation, the rats were fasted for 12 h and were only allowed free access to water. The Kyushu University Institutional Animal Care and Use Committee approved all animal protocols, according to the criteria outlined in the *Guide for the Care and Use of Laboratory Animals* prepared by the National Academy for Sciences and published by the National Institutes of Health (NIH).

Under ether anaesthesia, the abdomen was opened by a midline incision. Partial liver warm ischaemia, induced by clamping the hepatic hilar vessels that connect to the left lateral and median lobes, was performed for 90 min. The remaining lobes retained an intact portal and arterial blood supply, as well as venous drainage, preventing intestinal venous hypertension and bacterial translocation. The abdomen was closed and the animals were allowed to recover. After 90 min, the rats were again anaesthetized and a second laparotomy was performed. The microvascular clip was released and the abdomen was closed. Non-ischaemic lobes were not excised after reperfusion to allow comparison of the effect of dHGF on ischaemic lobes and non-ischaemic lobes separately, and to minimize deviation of biochemical data caused by hepatectomy. A total hepatic ischaemia model was not used to avoid the confounding effects of bowel ischaemia, although it would have more closely mimicked the clinical situation.

The rats were divided into two groups: dHGF group ($n = 36$) and control group ($n = 36$). The former group was given dHGF 0·5 mg/kg intravenously into the penile vein immediately after declamping, followed by 0·5 mg/kg every 12 h. The control group was given vehicle buffer. Because of the dose-dependent beneficial effect of dHGF in acute or chronic liver injury models[12,13], a high dose of dHGF was used in this study. Purified dHGF (Snow Brand Milk Products, Tochigi, Japan) was diluted with sodium chloride 0·15 mol/l, 0·03 per cent polysorbate 80 and sodium citrate 10 mmol/l.

Six animals in each group were killed at 1, 6 and 24 h, and at 2, 3 and 5 days after reperfusion. The wet liver weight per 100 g body-weight of the ischaemic and non-ischaemic lobes was measured separately. Blood samples were drawn from the vena cava, centrifuged immediately at 3000 r.p.m. for 10 min at 4°C, and were stored at −80°C until analysis. The liver specimens were fixed in 10 per cent neutral buffered formalin.

Biochemical measurements

Serum alanine transaminase (ALT), hyaluronic acid and albumin were assayed using standard enzymatic methods.

Histopathological examinations

Formalin-fixed liver specimens were embedded in paraffin. Sections 3 µm thick were stained with haematoxylin and eosin. The extent of hepatocellular necrosis was determined 24 h after reperfusion. Images of six separate stained slices were obtained as PICT files with a Fujix digital camera HC2500 3CCD and Photograb 2500 software (Fuji Film, Tokyo, Japan). The necrotic and total areas of each liver section were calculated using NIH image analysis software (Wayne Rasband, NIH, Bethesda, Maryland, USA), and the fraction of necrotic area compared with the total area of the liver section was determined.

The liver sections were deparaffinized and processed in an autoclave at 120°C for 1 min, after which they were incubated at 4°C overnight with monoclonal antibody raised against proliferating cell nuclear antigen (PCNA) (NCL-PCNA; Novocastra Laboratories, Newcastle upon Tyne, UK) diluted 1 : 100. The secondary biotinylated rabbit antimouse antibody and peroxidase-conjugated streptoavidin were from a Histofine SAB-PO (M) kit (Nichirei, Tokyo, Japan). After staining with diaminobenzidine, the slides were counterstained with haematoxylin, dehydrated and mounted. The proportion of cells expressing PCNA in the nucleus was calculated as the number of labelled cells with respect to the total number of calculated hepatocytes. Approximately 2000 non-necrotic hepatocytes were evaluated for each sample.

Terminal deoxynucleotidyl transferase-mediated 2′-deoxyuridine 5′-triphosphate (dUTP) nick end labelling (TUNEL) staining was performed using the Apop Taq *in situ* apoptosis detection kit (Oncor, Gaithersburg, Maryland, USA). The liver sections were deparaffined and digested in proteinase K (Nakarai Tasque, Kyoto, Japan) 20 µg/ml for 30 min at room temperature. Apop Taq equilibration buffer, working strength terminal deoxynucleotidyl transferase reaction mixture, stop/wash buffer and antidigoxigenin-dUTP were then applied in sequence. After staining with diaminobenzidine, the slides were counterstained with haematoxylin, dehydrated and mounted. An apoptosis index was calculated for each sample as the proportion of positive hepatocytes with respect to the total number of hepatocytes evaluated multiplied by 100. Only non-necrotic hepatocytes were quantified to determine the apoptotic index. Approximately 2000 hepatocytes were evaluated for each liver.

Statistical analysis

All values were expressed as mean(s.d.). Statistical analysis was performed using the Student's t test. $P < 0{\cdot}05$ was considered significant.

Table 1 Serum alanine aminotransferase, hyaluronic acid and albumin levels at different times following reperfusion

	1 h	6 h	24 h	2 days	3 days	5 days
ALT (units/l)						
Control	6188(948)	18 098(1132)	6949(1787)	–	–	–
dHGF	5489(591)	13 358(433)†	1021(83)†	–	–	–
Hyaluronic acid (ng/ml)						
Control	102(21)	202(13)	368(64)	–	–	–
dHGF	77(12)	182(12)	140(27)†	–	–	–
Albumin (g/dl)						
Control	–	–	3·9(0·2)	3·6(0·2)	3·9(0·2)	4·1(0·1)
dHGF	–	–	3·8(0·1)	4·2(0·3)†	4·3(0·2)*	4·5(0·1)†

Values are mean(s.d.). ALT, alanine aminotransferase; dHGF, deletion variant of hepatocyte growth factor. *$P < 0{\cdot}05$, †$P < 0{\cdot}01$ *versus* control value at same time interval

Table 2 Liver weight relative to body-weight at different times after reperfusion

	Liver weight (g per 100 g body-weight)			
	24 h	2 days	3 days	5 days
Ischaemic lobes				
Control	3·0(0·2)	3·2(0·3)	3·2(0·2)	3·0(0·1)
dHGF	3·1(0·3)	3·3(0·3)	3·7(0·1)*	3·5(0·2)†
Non-ischaemic lobes				
Control	1·3(0·1)	1·5(0·1)	1·4(0·2)	1·3(0·1)
dHGF	1·3(0·1)	1·8(0·1)*	1·9(0·2)†	1·9(0·2)†
Whole lobes				
Control	4·3(0·2)	4·8(0·3)	4·6(0·2)	4·3(0·1)
dHGF	4·5(0·4)	5·1(0·4)	5·6(0·3)†	5·5(0·2)†

Values are mean(s.d.). dHGF, deletion variant of hepatocyte growth factor. *$P < 0{\cdot}05$, †$P < 0{\cdot}01$ *versus* control value at same time interval

Results

Biochemical analysis

Following 90 min of hepatic warm ischaemia followed by reperfusion, ALT increased and peaked 6 h after reperfusion (*Table 1*). Compared with the vehicle-treated control group, dHGF significantly reduced ALT levels 6 and 24 h after reperfusion ($P < 0{\cdot}01$). After 24 h, ALT had returned close to baseline levels in the dHGF group, whereas it remained increased in the control group. Serum hyaluronic acid levels increased and peaked 24 h after reperfusion in the control group (*Table 1*). In the dHGF group, serum hyaluronic acid levels were significantly lower than those in the control group 24 h after reperfusion ($P < 0{\cdot}01$). Serum albumin decreased on the first postoperative day in both groups, but began to increase earlier in the dHGF group than the control group (*Table 1*).

Hepatocellular necrosis

Table 2 shows the proportion of necrotic area after 90 min of ischaemia and 24 h after reperfusion. The mean(s.d.) proportion of necrotic area was 61·9(7·3) and 85·6(6·4) per cent in the dHGF and control groups respectively after 90 min of ischaemia and 24 h of reperfusion ($P < 0{\cdot}01$).

Liver weight

The increase in the ischaemic-, non-ischaemic- and whole-liver weight : body-weight ratio after reperfusion in the dHGF group was greater than that in the control group (*Table 3*).

Assessment of hepatocyte regeneration

After reperfusion, the proportion of PCNA-positive hepatocytes in the non-ischaemic lobes increased and peaked on the second postoperative day in both groups (*Table 3*). In the ischaemic lobes, the proportion of PCNA-positive hepatocytes did not increase in both groups until 24 h after reperfusion and was significantly greater in the dHGF group 24 h after reperfusion.

Assessment of hepatocyte apoptosis

The apoptotic index increased and peaked 6 h after reperfusion (*Table 4*). By comparison with the vehicle-treated control group, dHGF significantly reduced the hepatic apoptotic index 6 h after reperfusion ($P < 0{\cdot}05$). At 24 h after reperfusion, the proportion of TUNEL-positive hepatocytes was decreased in both groups, and no significant difference was recognized. *Fig. 1* shows the reduced proportion of TUNEL-positive hepatocytes in the dHGF group compared with the control group. Necrotic areas with more peroxidase cytoplasmic staining were not noted before the onset of necrosis at 6 h.

Discussion

In this experiment, dHGF promoted hepatocyte regeneration and protein synthesis after IR injury as described

Table 3 Proportion of hepatocytes positive for proliferating cell nuclear antigen in the non-ischaemic and ischaemic lobes at different times after reperfusion

	PCNA-positive hepatocytes (%)					
	1 h	6 h	24 h	2 days	3 days	5 days
Non-ischaemic lobes						
Control	26·1(6·7)	35·0(6·3)	37·2(6·0)	43·2(2·0)	39·0(3·5)	33·7(2·1)
dHGF	25·8(3·3)	45·0(6·5)*	58·5(5·2)†	60·3(3·8)†	53·3(4·0)†	48·2(2·6)†
Ischaemic lobes						
Control	34·5(11·9)	29·8(9·7)	36·2(4·2)	39·6(3·4)	42·0(4·5)	47·3(7·2)
dHGF	35·0(9·4)	31·5(11·8)	56·2(9·3)†	61·8(6·2)†	64·3(6·9)†	57·7(7·5)†

Values are mean(s.d.). dHGF, deletion variant of hepatocyte growth factor; PCNA, proliferating cell nuclear antigen $^*P < 0·05$, $†P < 0·01$ *versus* control value at same time interval

Table 4 Hepatocyte apoptosis in the non-ischaemic lobes at different times following hepatic reperfusion

	Apoptotic hepatocytes (%)		
	1 h	6 h	24 h
Control	20·9(4·2)	53·6(8·1)	21·1(11·3)
dHGF	19·3(4·4)	30·0(3·6)*	14·9(5·8)

Values are mean(s.d.). dHGF, deletion variant of hepatocyte growth factor; $^*P < 0·05$ *versus* control value at same time interval

previously[7]. Several studies have recently investigated the cytoprotective effect of HGFs on hepatocytes using acute hepatitis models. Kaido *et al.*[9] reported that HGF prevented hepatic injury induced by lipopolysaccharide and carbon tetrachloride in rats. Ishiki *et al.*[10] showed that HGF not only had a hepatotrophic effect for liver regeneration but also a potent antihepatitis effect in rats using carbon tetrachloride- and naphthylisothiocyanate-induced hepatitis models. In the current IR injury model, dHGF significantly decreased serum ALT levels, indicating that dHGF has a protective effect on hepatocytes during hepatic IR injury.

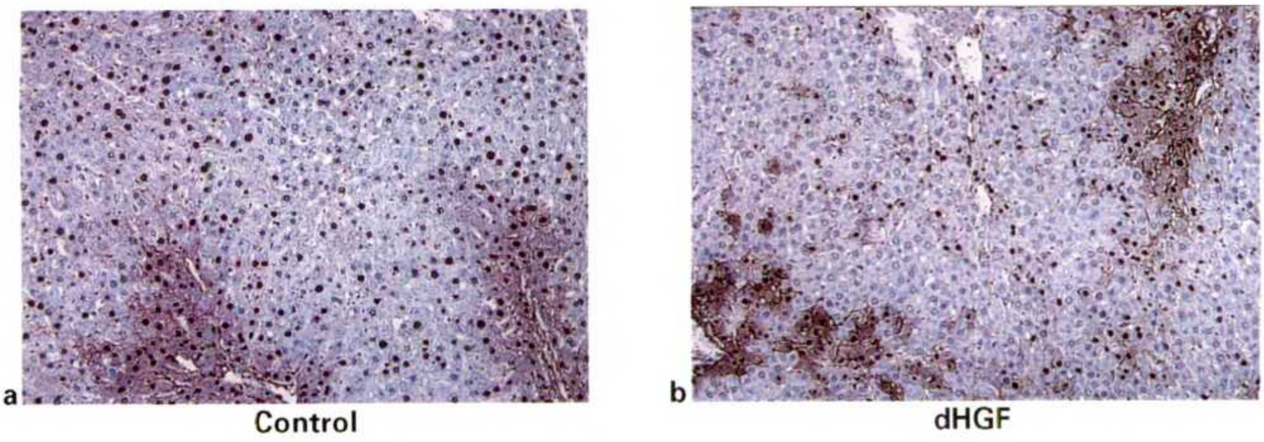

Fig. 1 Photomicrographs of terminal deoxynucleotidyl transferase-mediated 2′-deoxyuridine 5′-triphosphate nick end labelling 6 h after reperfusion in

a the control group and

b the group treated with the deletion variant of hepatocyte growth factor (dHGF).

The dark brown nuclei are apoptotic. Apoptotic hepatocytes were more prominent in the control group than in the dHGF group. Necrotic areas gave a slightly higher peroxidase background as noted by increased cytoplasmic staining. TUNEL stain; original magnification × 200

An increase in serum hyaluronic acid, which is degraded mainly by sinusoidal endothelial cells (SECs), indicates the dysfunction of SECs[14]. Yamashita *et al.*[12] have recently reported that dHGF reduced serum hyaluronic acid levels in models of rat cirrhosis, induced by dimethylnitrosamine or carbon tetrachloride. In the present IR injury model, dHGF significantly reduced the increase in both serum ALT and hyaluronic acid levels. Although dHGF has a direct hepatocyte protective effect[9,10], suppression of the serum transaminase rise after reperfusion in the dHGF group might be partly attributed to the protective effects of dHGF on SECs from IR injury and preservation of the sinusoidal microcirculation.

PCNA expression early after reperfusion was suppressed in the ischaemic lobes in both study groups. Schlossberg *et al.*[15] reported a possible decline in PCNA expression with the onset of apoptosis early after reperfusion in a murine hepatic IR injury model, and concluded that such cellular responses are influenced by the alternation in the patterning of immediate early genes, including c-*jun* and c-*fos*. Immediate hepatocellular responses might be geared toward reducing rather than promoting cellular proliferation soon after reperfusion.

Apoptosis was originally defined to describe the morphological changes in programmed cell death. Although IR injury was previously believed to result only in a necrotic pathway of cell death, it appears that apoptosis also has an important role in IR injury[16,17]. Furthermore, the extent of the apoptotic process after IR increases with the extent of necrosis and the increase in transaminase[15]. Although the exact mechanism responsible for hepatocyte apoptosis after IR is unclear, reactive oxygen species and acute reactant cytokines, including tumour necrosis factor α produced in the reperfused liver, have been implicated[1–4,16–18]. It has been reported that hepatocyte apoptosis in hepatic IR injury is executed within several hours[16].

Several reports also support the role of HGF as an important modulator of apoptosis. Miyazawa *et al.*[19] reported that hippocampal neuronal damage induced by forebrain ischaemia was prevented by HGF. The present study showed that dHGF prevented hepatocyte apoptosis 6 h after reperfusion, when apoptosis was recognized in the control group. Because several hours are required for HGF to exert a strong antiapoptotic effect[11], administration of dHGF immediately after reperfusion in this model might have effectively matched the peak of the hepatocyte apoptosis. Although the effect of dHGF administration 6 h before ischaemia was investigated in a preliminary test, it was less effective than that seen in the case of immediate postreperfusion treatment (data not shown). Activation of the HGF/c-*met* signalling pathway immediately after reperfusion may cause hepatocellular responses that are geared toward hepatocyte protection rather than hepatocyte regeneration.

It has also been reported that the transgenic expression of c-*met* makes hepatocytes resistant to apoptotic stimuli[20]. As to the intracellular mechanism of the inhibition of apoptosis by HGF, Kosai *et al.*[11] have reported that HGF creates an overexpression of Bcl-xL, a Bcl-2 antiapoptotic intracellular molecule family. These findings suggest that activation of the HGF/c-*met* signalling pathway would decrease the sensitivity of hepatocytes to multiple apoptotic stimuli including IR injury.

In conclusion, dHGF not only ameliorated IR injury but also accelerated recovery from these injuries. dHGF may be an effective pharmacological agent for treatment of clinical hepatic IR injury induced during hepatic resection and liver transplantation.

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Original article

Retrospective analysis of type of hepatic resection for hepatocellular carcinoma

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Background: Hepatic resection for hepatocellular carcinoma is now considered a relatively safe procedure, owing to refined surgical techniques and management.

Methods: Three hundred different types of hepatic resection performed in one hospital were reviewed retrospectively. The operative morbidity and mortality rates and long-term survival were assessed.

Results: Tumours were extirpated by lobectomy or extended lobectomy in 48 patients, by segmentectomy in 53, by subsegmentectomy in 94 and by partial resection in 105. The overall hospital mortality rate was 4 per cent (13 of 300). No operative death occurred after lobectomy or extended lobectomy. Segmentectomy and subsegmentectomy were associated with high postoperative complication and hospital mortality rates. There was a significant difference in survival rate between patients with and without a cancer-free surgical margin of more than 1·0 cm. The overall 5- and 9-year survival rates were 51 and 9 per cent respectively. Rates were 56 and 24 per cent for lobectomy or extended lobectomy.

Conclusion: For tumours of 2·1 cm or more in size lobectomy appears to carry the least risk of postoperative complications and death in hospital and best achieves a cancer-free surgical margin.

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Introduction

In Asia, most cases of hepatocellular carcinoma (HCC) occur in association with chronic parenchymal disease, particularly cirrhosis. The most common treatment for HCC is hepatic resection, but associated problems include high morbidity and mortality rates and a high recurrence rate[1,2]. The surgeon must thus aim to reduce postoperative complications, especially liver failure, to achieve long-term survival. The type of hepatic resection should be selected on the basis of hepatic functional reserve and neoplastic involvement. Although many studies have evaluated postoperative complications and survival rates after hepatic resection for HCC[3–5], there have been no reports analysing those associated with the specific types of hepatic resection. This paper describes clinical results, especially long-term survival and postoperative complications, according to the type of hepatic resection performed for 300 HCCs over an 10-year period.

Patients and methods

Hepatic resection was performed in 300 (54 per cent) of a total of 554 patients with HCC in this department between December 1987 and December 1997. Resections included those performed as initial treatments without prior arterial embolization or regional chemotherapy. The policy regarding indications for hepatic resection in HCC is based on the following: (1) a serum total bilirubin level of less than 2 mg/dl, (2) no ascites revealed by computed tomography or ultrasonography, (3) no more than two nodules and (4) an indocyanine green retention at 15 min ($ICG\,R_{15}$) of less than 30 per cent. If there were moderate or severe oesophageal varices occupying more than one-third of the oesophageal lumen, these were treated by endoscopic sclerotherapy before operation. All patients were followed on a monthly basis after surgery. When recurrence was detected, the patient was readmitted and several treatments were tried, such as further hepatic resection, arterial embolization, ethanol injection therapy and regional chemotherapy using a reservoir. Intra-abdominal bleeding, intra-abdominal infection, extra-abdominal infection, liver failure, upper gastrointestinal bleeding, prolonged bile leakage and uncontrolled ascites were classified as serious complications. Operative death was defined as death within 30 days after hepatic resection. Hospital death was defined as that occurring at any time during the first hospitalization.

The hospital mortality rate included all operative and hospital deaths.

Values are expressed as mean(s.d.). Mean values were compared by unpaired Student's t test and the χ^2 test was used to compare percentages. P < 0·05 was considered as significant. Cumulative survival rates determined or calculated by the Kaplan–Meier method were compared with the generalized Wilcoxon test.

Hepatic resection

Intraoperative ultrasonography was carried out to exclude the presence of other nodules and to localize the portal branches feeding the tumour. The operative procedures followed conventional terminology with respect to the eight subsegments of the liver designated by Couinaud[6]. Hepatic resections were classified as follows: lobectomy, resection of one hemiliver; extended lobectomy, additional segments in continuity; segmentectomy, resection of two Couinaud subsegments; subsegmentectomy, anatomical resection of one Couinaud subsegment; and partial resection, all other non-anatomical resections. To minimize intraoperative bleeding, Pringle's manoeuvre[7] involving vascular inflow occlusion was applied. Ischaemia was limited to periods of 15 min followed by 5 min of perfusion, which was repeated if necessary. For subsegmentectomy or partial resection, the technique of resection followed Makuuchi's procedure[8,9]. All parenchymal dissections for hepatic resection were performed by the forceps fracture method, without an ultrasonic dissector. Selection of the type of hepatic resection was dependent on hepatic functional reserve, location, size and number of nodules.

Results

There were 235 men and 65 women, with an overall mean(s.d.) age of 60·8(9·2) years. Among these 300 patients with HCC, tumours were extirpated by lobectomy or extended lobectomy in 48 patients, by segmentectomy in 53, by subsegmentectomy in 94 and by partial resection in 105. *Table 1* shows the laboratory data for all 300 patients. Liver cirrhosis and chronic hepatitis were recognized macroscopically and microscopically in 269 patients (90 per cent).

The preoperative clinical data are summarized in *Table 2* according to the type of hepatic resection performed. The ICG R_{15} for partial resection was significantly higher than that for other types of hepatic resection (P < 0·03). The ICG R_{15} for lobectomy or extended lobectomy was significantly lower than that for subsegmentectomy (P < 0·05), but there was no significant difference observed between lobectomy or extended lobectomy and segmentectomy. The cholinesterase and hepaplastin test values for partial resection were significantly lower than those for other types of hepatic resection (P < 0·03). Of 45 patients with a tumour size of less than 2·0 cm, partial resection was required in 22, subsegmentectomy in 21 and segmentectomy in two. Thirty-five (12 per cent) of 300 patients had two nodules and partial resection or subsegmentectomy was applied in the majority of them.

Table 1 Demographic and laboratory data for 300 patients who underwent hepatic resection

Age (years)*	60·8(9·2)
Sex ratio (M : F)	235 : 65
Virus infection†	
HBsAg positive	55 (18)
HCVAb positive	235 (79)
HBsAg and HCVAb positive	0 (0)
HBsAg and HCVAb negative	10 (3)
Liver cirrhosis and chronic hepatitis†	
Yes	269 (90)
No	31 (10)
Liver function parameters*	
ICG R_{15} (%)	15·6(8·6)
ZTT (units)	21·4(10·3)
Hepaplastine test (%)	79·7(17·0)
Cholinesterase (units/l)	243(117)
LCAT (units/l)	60·3(20·0)
α-Fetoprotein (ng/l)	1616(4236)

*Values are mean(s.d.); †values in parentheses are percentages. HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; ICG R_{15}, indocyanine green retention at 15 min; ZTT, zinc sulphate turbidity test; LCAT, lecithin cholesterol acyltransferase

As shown in *Table 3*, blood loss with lobectomy or extended lobectomy was significantly greater than that with other types of hepatic resection (P < 0·02). There was no significant difference in intraoperative blood transfusion requirements between lobectomy or extended lobectomy and segmentectomy (P = 0·089). The percentage of patients with a cancer-free margin of more than 1·0 cm was 75, 85, 75 and 94 per cent after partial resection, subsegmentectomy, segmentectomy, and lobectomy or extended lobectomy respectively. Lobectomy or extended lobectomy accounted for the greatest proportion of patients with a cancer-free margin of more than 1·0 cm (P < 0·05).

Postoperative complications developed after partial resection, subsegmentectomy, segmentectomy, and lobectomy or extended lobectomy in 23 per cent (24 of 105), 28 per cent (26 of 94), 40 per cent (21 of 53) and 15 per cent (7 of 48) of patients respectively (*Table 4*). Postoperative complications occurred significantly more often after segmentectomy than after other types of hepatic resection (P < 0·04). The overall incidence of intra-abdominal infection with hepatic resection was 11 per cent (34 of 300).

Table 2 Preoperative clinical data according to type of hepatic resection

	Partial resection (*n* = 105)	Subsegmentectomy (*n* = 94)	Segmentectomy (*n* = 53)	Lobectomy or extended lobectomy (*n* = 48)
Laboratory data*				
ICG R_{15} (%)	19·2(10·5)†	16·0(8·4)¶	13·8(7·0)	11·7(6·0)
Cholinesterase (units/l)	226(95)‡	243(127)	255(113)	281(127)
Hepaplastine test (%)	74·2(13·2)‡	80·5(16·5)	80·6(20·8)	80·9(20·1)
Features of HCC				
Tumour size (cm)				
≤2·0	22	21	2	0
2·1– 5·0	76	61	30	5
5·1– 10·0	7	12	20	19
>10·1	0	0	1	24
No. of tumours				
One	82	89	50	44
Two	23	5	3	4
Main location				
Left lateral segment	14	1	20	6
Middle segment	14	13	1	7
Anterior segment	45	58	14	21
Posterior segment	32	22	18	14

*Values are mean(s.d.). ICG R_{15}, indocyanine green retention at 15 min; HCC, hepatocellular carcinoma. †$P < 0·03$ *versus* other types of hepatic resection; ‡$P < 0·03$ *versus* other types of hepatic resection; ¶ $P < 0·05$ *versus* lobectomy or extended lobectomy

Table 3 Operative data according to type of hepatic resection

	Partial resection (*n* = 105)	Subsegmentectomy (*n* = 94)	Segmentectomy (*n* = 53)	Lobectomy or extended lobectomy (*n* = 48)
Operating time (min)*	276(99)	274(98)	316(128)	391(130)‡
Blood loss (ml)*	1088(994)	999(980)	1395(1424)	1407(1028)‡
Blood transfusion				
Yes†	30 (29)	44 (47)	23 (43)	34 (71)
No†	75 (71)	50 (53)	30 (57)	14 (29)
Volume (ml)*	320(705)	447(646)	600(1084)	710(1273)
FFP transfusion				
Yes†	84 (90)	67 (85)	30 (75)	47 (98)
No†	9 (10)	12 (15)	10 (25)	1 (2)
Volume (ml)*	523(398)	596(383)	681(539)	880(496)§
Surgical margin > 1·0 cm†				
Present	79 (75)	80 (85)	40 (75)	45 (94)¶
Absent	26 (25)	14 (15)	13 (25)	3 (6)

*Values are mean(s.d.); †values in parentheses are percentages. FFP, fresh frozen plasma. ‡$P < 0·02$ *versus* other types of hepatic resection; §$P < 0·05$ *versus* partial resection and subsegmentectomy; ¶$P < 0·05$ *versus* other types of hepatic resection

Segmentectomy was associated with a significantly higher incidence of intra-abdominal infection than other types of hepatic resection ($P < 0·01$). The incidence of prolonged bile leakage was significantly higher with subsegmentectomy and segmentectomy than with the other types of hepatic resection ($P < 0·01$). Operative death occurred with partial resection ($n = 1$), subsegmentectomy ($n = 1$) and segmentectomy ($n = 1$) but not with lobectomy or extended lobectomy. Hospital death occurred after subsegmentectomy ($n = 7$) and segmentectomy ($n = 3$), but not after partial resection and lobectomy or extended lobectomy. Thus, the overall hospital mortality rate was 4 per cent (13 of 300).

Survival

With partial resection, the 5- and 9-year cumulative survival rates were 42 and 20 per cent respectively. With subsegmentectomy, the corresponding values were 40 per cent and zero. Similarly, with segmentectomy they were 46 per

Table 4 Complications and deaths according to type of hepatic resection

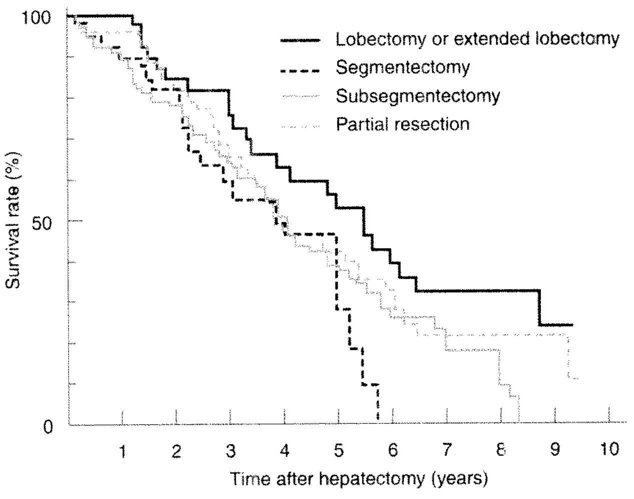
	Partial resection (n = 105)	Subsegmentectomy (n = 94)	Segmentectomy (n = 53)	Lobectomy or extended lobectomy (n = 48)
Complications				
Yes	24	26	21	7
No	81	68	32	41
Intra-abdominal bleeding	1	2	2	1
Intra-abdominal infection	11	11	10	2
Extra-abdominal infection	7	7	1	1
Upper GI tract bleeding	0	2	0	1
Prolonged bile leakage	0	3	4	1
Uncontrolled ascites	5	1	4	1
Hospital mortality				
Operative death	1	1	1	0
Hospital death	0	7	3	0

GI, gastrointestinal

cent and zero. However, the respective values for lobectomy or extended lobectomy were 56 and 24 per cent. The rates did not differ significantly between partial resection and lobectomy or extended lobectomy ($P = 0.2$); however, the survival rate after lobectomy or extended lobectomy was significantly higher than that after subsegmentectomy or segmentectomy ($P < 0.05$) (*Fig. 1*). *Fig. 2* shows the cumulative survival rates according to the presence or absence of a macroscopic cancer-free surgical margin of more than 1·0 cm. The 5- and 9-year survival rates for patients with a macroscopic cancer-free surgical margin of more than 1·0 cm were 55 and 21 per cent respectively. In the absence of a macroscopic 1·0-cm cancer-free surgical margin, the corresponding rates were 29 per cent and zero. There was a significant difference between the two groups in terms of the cumulative survival rate ($P = 0.0125$).

Discussion

In the present study, postoperative complications and long-term survival were analysed retrospectively in patients with various types of hepatic resection, and an attempt



Lobectomy or extended lobectomy	48	48	39	38	28	22	19	10	8	7
Segmentectomy	53	45	42	32	21	6				
Subsegmentectomy	94	85	78	62	45	35	24	15	10	
Partial resection	105	101	86	69	46	43	30	18	16	10

Fig. 1 Cumulative survival rates (Kaplan–Meier method) after the four types of hepatic resection. The 5-, 7- and 9-year cumulative survival rates were 42, 20 and 20 per cent respectively after partial resection, 40 per cent, 22 per cent and zero after subsegmentectomy, 46 per cent, zero and zero after segmentectomy, and 56, 33 and 24 per cent after lobectomy or extended lobectomy

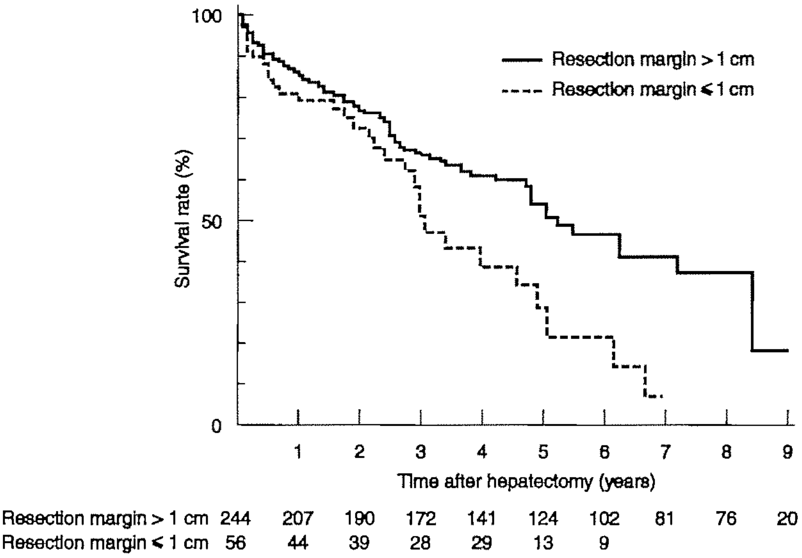


Fig. 2 Cumulative survival rates (Kaplan–Meier method) for those with and without a surgical margin of more than 1·0 cm. The cumulative survival rates at 5, 7 and 9 years were 55, 44 and 21 per cent respectively in patients with a surgical margin of more than 1·0 cm. For patients with a surgical margin of 1·0 cm or less the corresponding rates were 29 per cent, zero and zero. There was a significant difference in survival rate between the two groups ($P = 0{\cdot}0125$, Wilcoxon test)

was made to establish guidelines for choosing between the various options for optimal surgical treatment of HCC.

The extent of hepatic resection is estimated tentatively from tumour size, location and liver function. Subsegmentectomy with dissection from the root of the cancer-bearing subsegmental portal branch is thus a reasonable method of hepatic resection from the curative point of view. However, the hospital mortality rate was significantly higher in the subsegmentectomy group in this series. The causes were postoperative intra-abdominal infection, probably due to a large cut surface, together with insufficient drainage. The incidence of infection with subsegmentectomy for the anteriosuperior segment was particularly high. Segmentectomy exhibited the highest postoperative complication rate, particularly anterior and posterior segmentectomy. Lateral segmentectomy is easy to perform anatomically, and postoperative complications were almost absent in this series. Maximum efforts should be made to prevent bile leakage in such segmentectomies, and continuous-suction drainage should be considered. Lobectomy or extended lobectomy exhibited the lowest postoperative complication rate, and serious intra-abdominal infection did not occur. This may reflect the fact that lobectomy is the most anatomical hepatic resection, resulting in a small cut surface. It is a safe technique for patients with a good hepatic functional reserve, with an ICG R_{15} value of 20 per cent or lower. Partial resection is associated with a low incidence of operative complications compared with subsegmentectomy or segmentectomy. As a result, mortality and morbidity rates are low. However, with this procedure it is relatively difficult to guarantee a cancer-free surgical margin of more than 1·0 cm.

Thirteen (4 per cent) of 300 patients who underwent hepatic resection died in hospital. The main cause of death was intra-abdominal infection, which occurred in eight of the 13 patients. Intra-abdominal infection was the most critical factor for liver failure following hepatic resection[10]. Liver cirrhosis with weak reticuloendothelial function and massive bleeding during operation can lead to intra-abdominal infection. To prevent such infection, the authors consider it necessary to select a hepatic resection procedure with a small cut surface, to prevent bile leakage, and to reduce haemorrhage during the operation[10,11]. Viewed in this light, lobectomy seems to be an ideal procedure.

Although hepatic resection is the most radical treatment for HCC, a high rate of recurrence or recrudescence is noted[12–14], and the remnant liver is the site of recurrence in most patients. Numerous studies have already described prognostic features such as tumour size, portal venous infiltration, capsular infiltration and intrahepatic metastasis[15–17]. Concerning surgical factors, attention has been given to the cancer-free surgical margin (more than 1·0 cm) and the extent of hepatic resection. In the present study there was a significant difference in survival rates between patients with and without a cancer-free margin of more than 1·0 cm. It is important to ensure a surgical margin of more than 1·0 cm in order to achieve long-term survival following hepatic resection[18,19]. Reviewing the techniques in terms of attaining a cancer-free margin of more than 1·0 cm, partial resection yielded the lowest proportion of satisfactory margins and lobectomy or extended lobectomy yielded the highest. As a result, the long-term survival rate of patients who underwent lobectomy or extended lobectomy was excellent.

This finding confirms that lobectomy or extended lobectomy should be performed if possible in patients with a unifocal HCC over 2·1 cm in diameter. However, HCCs less than 2·0 cm in diameter seem to be treated adequately by partial resection. The survival rate of patients with HCC less than 2·0 cm in diameter who undergo hepatic resection is excellent. In this series, the long-term survival rate of patients who underwent partial resection, including 21 per cent with HCCs less than 2·0 cm in diameter, was relatively good.

The cause of intrahepatic recurrence of HCC is thought to be implantation of cancer cells carried by the cancer-bearing branch of the portal vein of the nearby hepatic segments[8]. This suggests that complete hepatic unilobar resection will affect the recurrence rate positively. In circumstances in which lobectomy can ensure a consistent cancer-free surgical margin of more than 1·0 cm, it seems to be an ideal procedure in terms of reduced mortality and morbidity rates and long-term survival.

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Original article

Experimental study of the influence of endoleak size on pressure in the aneurysm sac and the consequences of thrombosis

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Background: This was an experimental study of endovascular aortic surgery, looking at the relationship between the size of an endoleak, pressure in the aneurysm sac and the effect of thrombosis produced by coagulation.
Methods: In three pigs, 16 saccular aneurysms were connected to the aorta by various side branches with different diameters and lengths ('endoleaks'). Mean and pulse pressures were measured in the systemic circulation as well as in the aneurysm sac during the experiment. Duplex ultrasonography was used to determine whether the endoleak and the aneurysm were patent or thrombosed. Thrombosis was influenced by systemic tranexamic acid, fibrinogen in the aneurysm sac, Gelfoam in both endoleak and aneurysm sac, and by Histoacryl glue in the endoleak.
Results: With an open endoleak, the mean pressure in the aneurysm and the aorta was identical. Mean aneurysm pressure was lower with a thrombosed endoleak and was related to the diameter of the endoleak. Pulse pressure was recorded in the aneurysm sac when there was an open endoleak and a non-thrombosed aneurysm, and was related to the diameter of the open endoleak. Thrombosed endoleaks never produced pulse pressure in the aneurysm. If Histoacryl and Gelfoam induced thrombosis of the endoleak, the decrease in mean aneurysm pressure was identical to that resulting from the spontaneous thrombosis of endoleaks.
Conclusion: An open endoleak results in systemic arterial pressure in the aneurysm sac. Pulse pressure is detected if the aneurysm is patent, but absent if there is complete or partial thrombosis of the aneurysm. Endoleak thrombosis, either spontaneous or by embolization, is accompanied by a decrease in mean pressure and the absence of pulse pressure in the aneurysm sac. The extent to which these experimental findings are comparable to the clinical situation represents a field of further research.

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Introduction

In selected patients an aneurysm of the abdominal aorta can be excluded successfully by placement of an endovascular graft via the femoral arteries. A frequent complication of this treatment is the occurrence of an endoleak[1]. An endoleak is defined as flow between the stent-graft and the wall of the aneurysm[2,3]. Endoleaks are usually situated at the proximal stent attachment site and produce a small perigraft channel with outflow through a partially thrombosed aneurysm sac[4]. These endoleaks can cause progressive enlargement of the aneurysm and may eventually result in rupture. The relation between the size of an endoleak, the level of aneurysm pressure, and both enlargement and rupture of the aneurysm sac is unknown.

Some endoleaks, however, are not associated with an increase in the diameter of the aneurysm at follow-up and probably do not need intervention. Even when an endoleak is not detected, aneurysm diameter can still increase during follow-up[5]. From past experience, it is known that a thrombosed aneurysm of the abdominal aorta, produced by ligating the iliac arteries, can still result in rupture of the aneurysm[6]. In this situation, the thrombus forms a diaphragm just beneath the renal arteries and must conduct pressure high enough to lead to aneurysm rupture. The same mechanism in a thrombosed endoleak may be responsible for aneurysm enlargement without a visible endoleak. The relationship between the diameter and length of the thrombosed endoleak and the level of pressure conduction is unknown.

The objective of this study was to determine the effect of the length and diameter of open and thrombosed endoleaks on the mean pressure level and pulsatile flow in the aneurysm sac in order to help determine which endoleaks need treatment. Furthermore, the effects of manipulation of thrombus quality and composition, using tranexamic acid and fibrinogen, on both parameters were evaluated. Finally, the effect on pressure of occluding an endoleak with Histoacryl glue (B. Braun, Melsungen, Germany) and Gelfoam (Pharmacia and Upjohn, Woerden, The Netherlands) was studied.

Materials and methods

In the clinical situation, after endovascular repair of an abdominal aortic aneurysm, a perigraft endoleak consists of a channel between the stent attachment site and the aortic wall. This channel leads to the aneurysm sac and can be either open, or partially or completely thrombosed.

Aneurysm model

Thoracic aortas from 80–90-kg pigs were obtained from the abattoir and stored in the refrigerator at – 80°C for 2 weeks until the time of experimentation. Intercostal side branches were ligated. Ten-centimetre lengths were closed at both ends with running 6/0 polypropylene sutures. The diameter of the aneurysms was approximately 18 mm, so the ratio of aneurysm to infrarenal aortic diameter was about 3 (*Fig. 1*). This situation represented a human with a 5–6-cm diameter infrarenal aortic aneurysm. The volume of all aneurysms was kept at approximately 10 ml. Patency of the aneurysm model was determined by duplex imaging.

Endoleak model

This situation was simulated by connecting an artificial saccular aneurysm to the native aorta. An endoleak was simulated by an aortic side branch to which the aneurysm was connected (*Fig. 1*). No outflow channel was provided. By choosing different side branches and varying the length of the side branches, endoleaks of different diameter and length could be evaluated. Length and diameter of the endoleaks was determined by duplex ultrasonography. The patency of the endoleak was visualized similarly.

Surgical procedures

Three pigs with a mean weight of 67·6 (range 65·6–69·6) kg underwent operative procedures. After premedication with Stresnil (Boehringer Ingelheim, Alkmaar, The Netherlands) 2 mg/kg and atropine 0·05 mg/kg, the pigs were anaesthetized with intravenous Nesdonal (Rhône-Poulenc Rorer, Amstelveen, The Netherlands) 10 mg/kg and intubated. Anaesthesia was continued with 60 per cent nitrous oxide, 40 per cent oxygen and 0·5–3 per cent isoflurane. Muscle relaxation was achieved with Pavulon

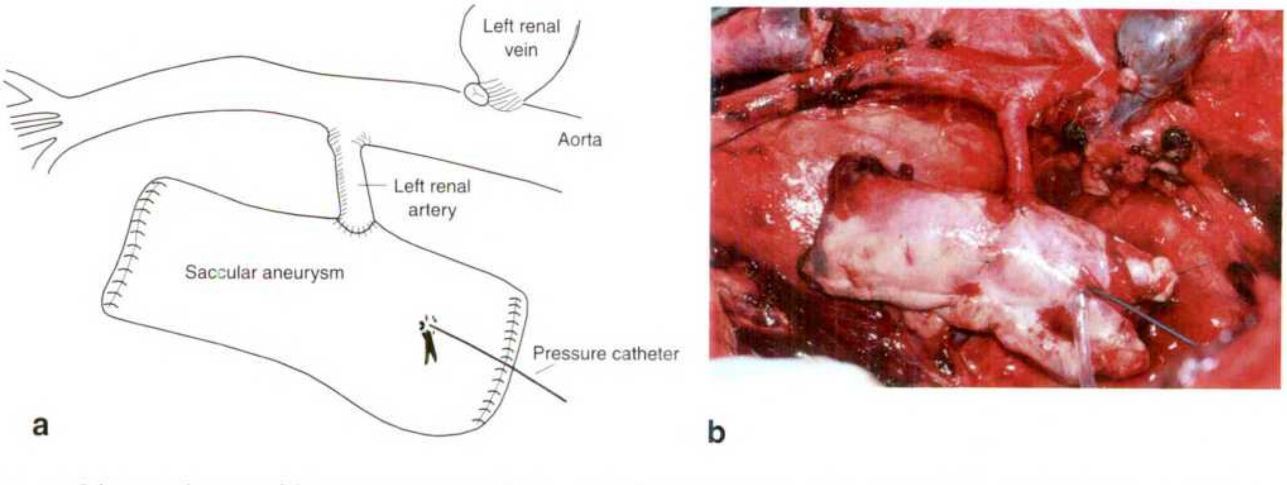

Fig. 1 **a** Schematic drawing of the aneurysm and endoleak model. The left kidney has been removed. The artificial aneurysm has been connected to the left renal artery. A pressure catheter is *in situ* in the aneurysm. Right side is cranial.
b Operative photograph

(Organon Nederland, Oss, The Netherlands) 4 mg, with an additional 2 mg if necessary. The pigs were placed supine. The aorta was exposed along its length with a left thoracoabdominal incision to allow the various side branches to be used. The experiments were performed according to the rules of the Animal Experimental Committee of the Leiden University Medical Centre. The pigs were killed directly after the experiments.

Aneurysm implantation

After dissection of the chosen aortic side branch and selection of a suitable length, the side branch was clamped with a bulldog clip and transected. The distal end of the side branch was ligated. An anastomosis was constructed between the side branch and an artificial pig thoracic aortic aneurysm using a running 6/0 suture.

In the three pigs, 16 artificial aneurysms could be evaluated after anastomosing to aortic side branches of varying length and diameter ($n = 15$) and end–side to the aorta ($n = 1$). The arteries used were coeliac trunk ($n = 1$), splenic artery ($n = 1$), renal artery ($n = 5$), inferior mesenteric artery ($n = 3$), common iliac artery ($n = 5$) and sacral artery ($n = 1$).

The diameter of the endoleak varied from 1·4 to 8·7 (mean 3·6) mm. The mean length of the endoleak was 20·5 (range 1·0–41·0) mm. The calculated volume of the endoleaks ($(0{\cdot}5 \times \text{diameter})^2\Pi \times \text{length}$) varied from 40 to 4800 (mean 2200) mm^3. The endoleak diameters were chosen to match established diameters of perigraft endoleaks caused by folding[7] and diameters of fabric defect endoleaks investigated by others[8].

Pressure measurements

After re-establishing the circulation to the side branch, a pressure catheter (MicroTransducer Catheter; Dräger Medical Electronics, Best, The Netherlands) was inserted into the aneurysm and pressure measurements were performed. Subsequently, without restriction of flow, the aneurysm was observed until it and the endoleak thrombosed; pressure measurements from the aneurysm were taken again. Pressure measurements were repeated during the experiment, for up to 6 h after the aneurysm was connected the systemic circulation. The systemic pressure was measured continuously with a similar pressure catheter which was introduced via the right carotid artery into the descending thoracic aorta.

In the systemic circulation and aneurysm sac, systolic, diastolic, mean and pulse pressures were recorded. A total of 63 pressure measurements was performed; the number per aneurysm varied from 2 to 6 (mean 4).

Endoleak closure

The effect of influencing the thrombosis of the endoleak on pressure measurements was evaluated by adding systemic medication or local products.

In the first pig (control), thrombus formation in the artificial aneurysms was not influenced either by changing the composition of the blood in the aneurysm or by adding medication.

The second pig was given tranexamic acid (Cyclokapron 100 mg/ml; Pharmacia and Upjohn) 1000 mg intravenously starting directly after intubation and repeated 6 h after the first dose. The purpose of this medication was to evaluate the effect of inhibition of fibrinolysis and its effect on pressure transmission. Patterson and Harpel[9] have demonstrated that inhibiting fibrinolysis within a clot makes the thrombus more stable and resistant to pressure transmission. The dose used was identical to that advised for the treatment of systemic fibrinolysis in humans according to body-weight.

In the third pig, the side branch to the aneurysm was reclamped after the initial pressure measurements and 45 mg fibrinogen (Clottagen 1·5 g per 100 ml; LFB, Courtaboeuf, France) was added to the blood of the saccular aneurysm 1 min before the clamp on the side branch was removed again. The plasma fibrinogen level is 2–4·5 mg/ml in humans. The objective was at least to double the concentration of fibrinogen in the blood within the aneurysm. This was achieved by replacing 3 ml of blood in the aneurysm sac (containing 10 ml) with 3 ml of human fibrinogen 15 mg/ml.

In the pig that did not undergo manipulation of coagulation, the effect of closing an endoleak with Gelfoam was evaluated. The thrombus was removed from three aneurysms and endoleaks through an arteriotomy in the aneurysm and refilled with pieces of Gelfoam. After suture closure of the aneurysm, the circulation to the aneurysm sac was re-established and pressure measurements were repeated. Similarly, three further endoleaks and aneurysms in the control pig were cleared of thrombus. Using a puncture technique through the aneurysm, the endoleak was occluded by injecting Histoacryl glue. Again, pressure measurements were repeated.

Thromboelastography

Blood samples were taken from the aneurysm directly after recirculation in the control pig and in the pig given tranexamic acid, and directly after adding fibrinogen to the aneurysms. The clotting mechanism was evaluated by thromboelastography (TEG). The effect of tranexamic acid on reducing fibrinolysis and the effect of adding extra fibrinogen to the aneurysm on the clotting mechanism were evaluated by TEG.

Table 1 Pressure measurements in the systemic circulation and the aneurysm sac

	Open endoleak			Partially thrombosed endoleak		Thrombosed endoleak
	Open aneurysm ($n=26$)	Partially thrombosed aneurysm ($n=3$)	Thrombosed aneurysm ($n=8$)	Partially thrombosed aneurysm ($n=1$)	Thrombosed aneurysm ($n=5$)	Thrombosed aneurysm ($n=20$)
Mean pressure (mmHg)						
Systemic	83(14) (64–115)	81(10) (70–91)	83(17) (62–118)	75	71(11) (53–78)	74(10) (43–89)
Aneurysm	84(13) (67–116)	69(26) (40–86)	78(30) (35–127)	72	68(8) (59–78)	32(25) (1–86)
Pulse pressure (mmHg)						
Systemic	16(5) (10–25)	18(8) (11–26)	18(6) (12–27)	15	19(4) (15–22)	16(3) (11–22)
Aneurysm	12(8) (0–30)	0(0) (0)	0(0) (0)	0	2(4) (0–8)	0(0) (0)

Values are mean(s.d.) (range)

Statistical analysis

SPSS 8.0 for Windows (SPSS, Chicago, Illinois, USA) was used for statistical calculations. Pearson's correlation coefficient was used to measure the linear association between the pressure and diameter of the endoleaks. The Wilcoxon signed rank test was used to determine differences between aneurysm and systemic pressures. Statistical significance was defined as $P < 0.05$.

Results

Mean aneurysm pressure

The mean aneurysm pressure with an open endoleak and a non-thrombosed aneurysm sac was 84 mmHg (*Table 1*). For partially and completely thrombosed aneurysms, both with an open endoleak, mean pressure within the aneurysm was 69 and 78 mmHg respectively. The mean pressure in the aneurysm of all groups with an open endoleak did not differ significantly from the systemic mean arterial pressure (*Fig. 2*).

When the aneurysm thrombosed with partial thrombosis of the endoleak, the mean aneurysm pressure was 68 mmHg. After thrombosis of both aneurysm and endoleak, the mean aneurysm pressure was reduced to 32 mmHg (*Fig. 3*). In this situation a decrease in mean aneurysm pressure occurred the moment after thrombosis of the endoleak (*Fig. 4*).

Aneurysm pulse pressure

Mean aneurysm pulse pressure for both open aneurysm and endoleak was 12 mmHg (*Table 1*). There was no significant difference between aneurysm and systemic pulse pressure. Aneurysm pulse pressure was absent in all experiments with an open endoleak combined with either a partially or completely thrombosed aneurysm (*Fig. 5*).

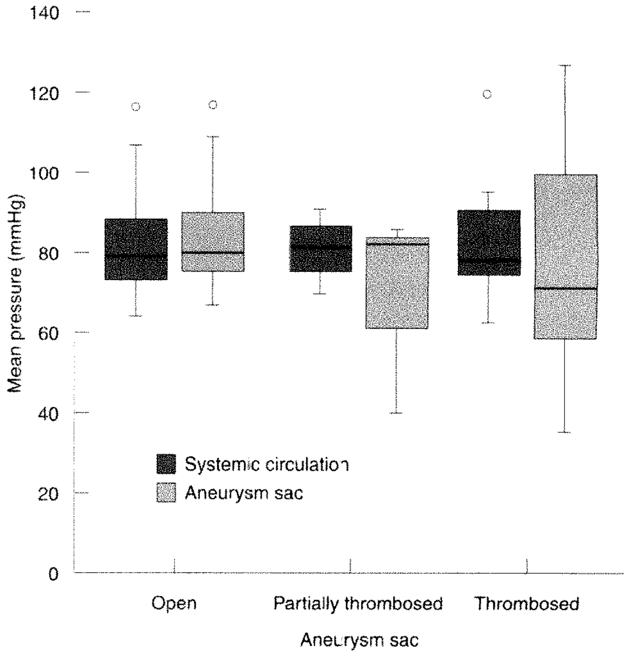

Fig. 2 Mean pressure in the aneurysm sac and systemic circulation in experiments with an open endoleak with respect to open ($n = 26$), partially thrombosed ($n = 3$) and completely thrombosed ($n = 8$) aneurysms. Median values are shown as thick horizontal lines, boxes represent 25–75th percentiles and 10–90th percentiles are indicated by bars; outliers are also shown (○). There were no significant differences between pressures in the aneurysm sac and the systemic circulation

A pulse pressure of 8 mmHg was observed in only one thrombosed aneurysm with partial thrombosis of the endoleak. In the remaining experiments, the pulse pressure was zero. For all thrombosed endoleaks, the aneurysm pulse pressure was zero.

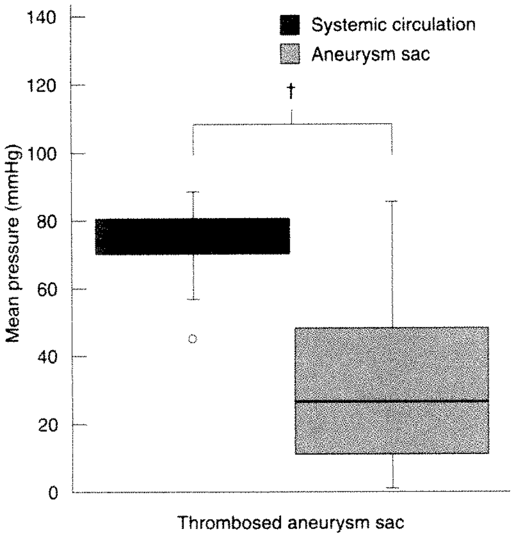

Fig. 3 Mean pressure in the systemic circulation and aneurysm sac when there was a thrombosed endoleak and a completely thrombosed aneurysm. Median values are shown as thick horizontal lines, boxes represent 25–75th percentiles and 10–90th percentiles are indicated by bars; an outlier is also shown (○). †$P < 0.001$ (Wilcoxon signed rank test)

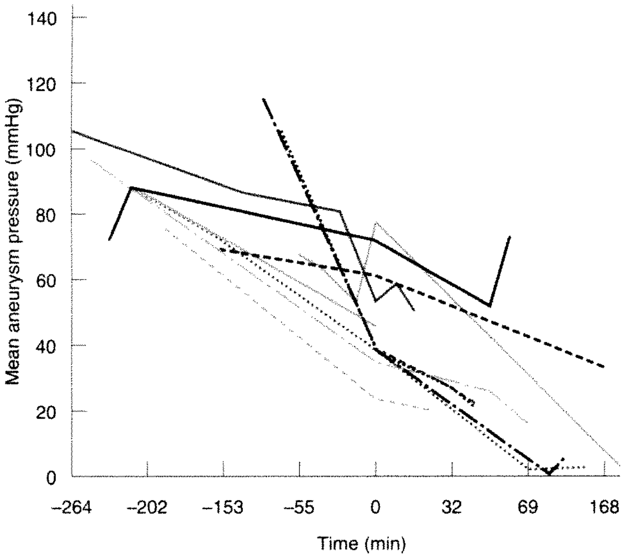

Fig. 4 Change in mean aneurysm pressure with time in experiments with a thrombosed endoleak. Time point zero denotes the first pressure measurement with a thrombosed endoleak, as determined by ultrasonography. One endoleak partially reopened after earlier thrombosis and the mean aneurysm pressure rose again (———)

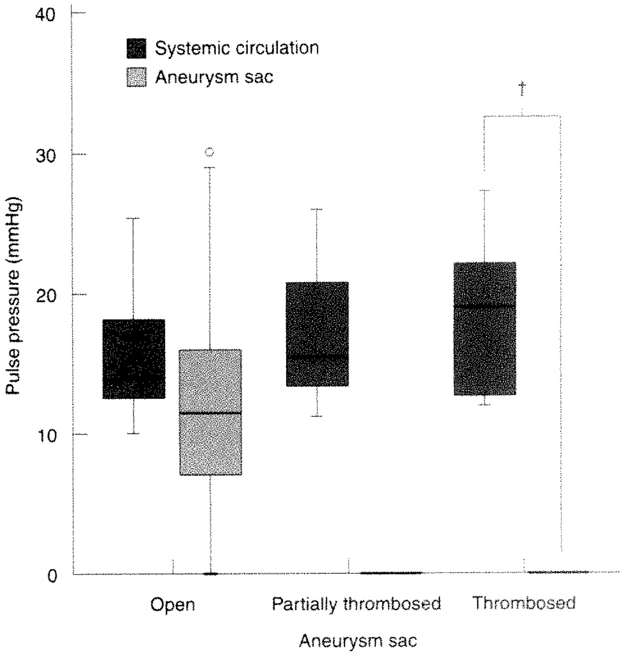

Fig. 5 Pulse pressure in the aneurysm sac and in the systemic circulation in experiments with an open endoleak with respect to open ($n = 26$), partially thrombosed ($n = 3$) and completely thrombosed ($n = 8$) aneurysms. Median values are shown as thick horizontal lines, boxes represent 25–75th percentiles and 10–90th percentiles are indicated by bars; an outlier is also shown (○). †$P = 0.012$ (Wilcoxon signed rank test)

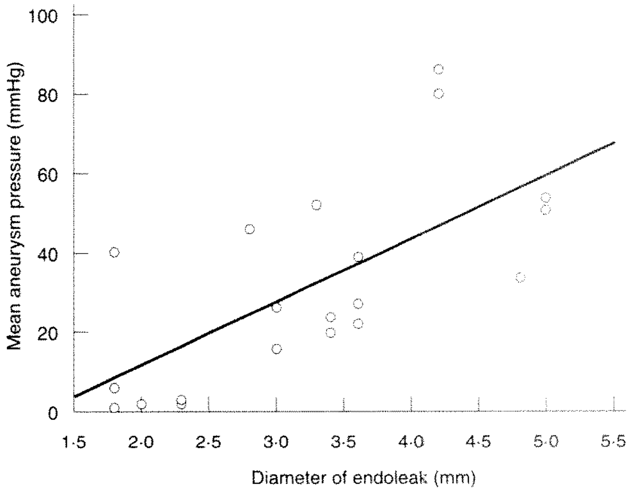

Fig. 6 Relation between the mean aneurysm pressure after thrombosis of the endoleak and the diameter of the thrombosed endoleak. $r = 0.67$, $P = 0.001$

Size of endoleak

After first opening the anastomosis between the side branch and the aneurysm, there was no significant correlation between mean pressure inside the sac and diameter, length and volume of the endoleak within the range tested. For thrombosed endoleaks, a significant correlation existed between mean pressure and endoleak diameter ($r = 0.67$,

$P = 0.001$) (*Fig. 6*), and endoleak length ($r = 0.61$, $P = 0.004$) but not endoleak volume ($r = -0.028$, $P = 0.91$).

Measurement of pressure in the aneurysm sac directly after connecting the aneurysm to the pig aorta showed a significant correlation between the pulse pressure and the diameter of the endoleak ($r = 0.62$, $P = 0.01$). The same correlation for endoleak volume and length was not observed ($r = 0.40$, $P = 0.13$ and $r = -0.21$, $P = 0.45$ respectively). The lack of pulse pressure inside the aneurysm sac when the endoleak was thrombosed suggests that this variable is independent of endoleak diameter.

In three experiments, after removal of the thrombus from the aneurysm, the pressure catheter was inserted into the thrombosed endoleak towards the aorta. The pressure in the thrombus remained low, but in the last few millimetres before entering the aorta, the pressure level suddenly increased up to systemic level and pulsatility returned immediately.

Thromboelastography

TEG in the control pig showed normal coagulation without any sign of fibrinolysis for up to 3 h. As expected, infusion of tranexamic acid did not influence systemic coagulation. The addition of extra human fibrinogen into the aneurysm sac prohibited the formation of thrombus inside the aneurysm. The thromboelastogram of blood with added fibrinogen showed a slim straight line, implying the absence of coagulation.

If an open or reopened endoleak was occluded by filling both the aneurysm and endoleak with Gelfoam ($n = 3$) or occluding the endoleak with Histoacryl glue ($n = 3$), the pressure measurements were identical to those performed shortly after spontaneous occlusion of the endoleak by thrombus. Mean aneurysm pressure remained high soon after occlusion, but pulse pressure in the aneurysm was absent.

After opening the aneurysm and removing the thrombus, the Histoacryl plug was easily dislodged. The Histoacryl plug was never firmly glued to the vessel wall and could be removed easily.

Discussion

An important finding of this study is that an open endoleak produces a mean pressure inside the aneurysm identical to that in the systemic circulation. This level of aneurysm pressure is independent of the size of the endoleak. These results confirm those of an *in vitro* study, in which very small endoleaks, not visualized by digital subtraction angiography or computed tomographic angiography, produced systemic pressure levels in an aneurysm sac[10]. In addition, whether or not the aneurysm sac was thrombosed did not influence the level of pressure within the sac, as long as the endoleak was open. As soon as the endoleak thrombosed, the mean aneurysm pressure declined to near zero.

The fact that thrombus can conduct pressure is well known. A thrombosed abdominal aortic aneurysm can still rupture because of the conduction of pressure through the thrombus[6,11]. In this situation, the diameter of the pressure-conducting thrombus is the diameter of the infrarenal aorta.

In these experiments, the endoleak with the largest diameter was an end-to-side anastomosis of the artificial aneurysm to the aorta. This endoleak did not thrombose during the time of the experiment. Aneurysms and endoleaks that did thrombose had a smaller endoleak diameter. In the latter group, a partial thrombosis was briefly seen in a small number. In the clinical situation, this condition probably also exists, but only for a short time.

With a patent endoleak, the difference between systolic and diastolic pressure within the aneurysm sac was clearly related to the absence or presence of thrombus in the aneurysm sac. In the absence of thrombus, the systemic and aneurysm pulse pressures were identical. The role of the pulse pressure as a risk for aneurysm rupture is not clear. However, a relation between pulse pressure and the rupture of saccular aneurysms was suggested in an *in vitro* model[12].

Another important finding of this study was the relation between pulse pressure in a non-thrombosed aneurysm sac and the diameter of a patent endoleak. The belief that large endoleaks are more dangerous than small ones might be explained not by the higher pressure in the aneurysm sac but by the presence of a pulsatile pressure.

When the endoleak thrombosed, the diameter of the endoleak was correlated to the mean aneurysm pressure. This finding was influenced by the fact that larger endoleaks tended to thrombose later in the experiment and thus there was less time in which to record a decrease in mean aneurysm pressure. It is uncertain whether the mean pressure in the aneurysms with the largest endoleaks would have declined to zero.

The exact size of endoleaks in humans is unknown and cannot yet be measured. Directly after stent-graft implantation, folding of the prosthesis with the formation of perigraft channels can cause perigraft endoleak. With standard 4-mm oversizing, these folds are approximately 2–3 mm in diameter[13]. The diameter of endoleaks in these experiments varied from 1·4 to 8·7 mm, which included this range.

The occlusion of endoleaks by either Histoacryl glue or Gelfoam resulted in identical pressure readings to those associated with spontaneous thrombosis. These findings suggest that embolization of a perigraft endoleak, which results in thrombosis of both the endoleak and the aneurysm sac, should prevent the course of progressive aneurysm growth and rupture[14–17]. However, progressive aneurysm enlargement and rupture has been reported in the absence of an endoleak[5,18,19]. This situation may result from a thrombosed endoleak conducting pressure to the aneurysm sac. White *et al.*[20] proposed the term 'endopressure' for this new type of endoleak.

If an endoleak is caused by a defect in the graft fabric, there is no length of the endoleak channel and embolization will result in thrombosis of the aneurysm sac but not the endoleak. In this situation the endoleak will not be visible, but the aneurysm pressure will not decline[8]. Additional stent-graft placement or conversion to open repair may be indicated in these patients.

Clinically an open endoleak and thrombosed aneurysm sac may be created by inducing thrombosis of the aneurysm with Gelfoam insertion into the sac during initial stent-graft treatment. This additional manoeuvre will not reduce mean aneurysm pressure unless thrombosis of the endoleak occurs, and has no place in stent-graft treatment of abdominal aortic aneurysms. If an endoleak can be embolized by Gelfoam or Histoacryl glue, this will result in decreased mean aneurysm pressure.

In the present study, influencing the clotting mechanism by both tranexamic acid and human fibrinogen did not have the results expected. Patterson and Harpel[9] noticed a positive effect of tranexamic acid on pressure resistance of the clot in rats. In the present experiments, there was no effect on pressure measurements or on TEG. Differences in the clotting mechanisms between rat and pig may be responsible for this discrepancy. Because no difference in systemic clotting parameters could be demonstrated by TEG between the control pigs and those given tranexamic acid or fibrinogen, the systemic and aneurysm pressure measurements could be analysed together. Local administration of human fibrinogen into a saccular aneurysm of the pig resulted in the inability of the blood to clot. This effect, to the authors' knowledge, has not been reported in the literature previously.

The present model investigated only the situation of an endoleak without an outflow tract. In the clinical situation, in most endoleaks, an outflow tract cannot be demonstrated[4]. This restriction was made because experiments evaluating both inflow and outflow variables would have been too complex to perform and interpret.

In conclusion, an open endoleak results in systemic mean pressure inside the aneurysm sac. If the aneurysm is not thrombosed, pulse pressure is present within the sac, but the magnitude depends on the diameter of the endoleak. Pulse pressure is absent within the aneurysm sac when it is completely or partially thrombosed. A thrombosed endoleak results in a decrease in mean pressure and the absence of pulse pressure in the aneurysm sac. The pressure decrease is more evident for smaller endoleaks. Successful embolization of an endoleak by Histoacryl glue or Gelfoam reduces the mean pressure in the aneurysm sac and may be a useful therapeutic option when there is progressive aneurysm growth. The extent to which these findings in an animal model are comparable to the clinical situation represents a field of further research.

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Original article

Management of proximal axillary and subclavian artery injuries

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Background: The aim of this study was to review the management and outcome of proximal axillary and subclavian artery injuries, and to estimate the prehospital mortality rate for subclavian injury through forensic pathology autopsy data.

Methods: Data were collected prospectively for 260 patients who presented between 1977 and 1996 with trauma to the proximal axillary and subclavian arteries.

Results: The majority of victims (214, 82 per cent) were admitted following stab injury. Some 154 patients (59 per cent) presented within 24 h of sustaining an injury and, of these, 59 (38 per cent) required immediate surgery. An additional 67 patients (26 per cent) attended 2 days or more after injury. Comparison of these data with those from forensic autopsy reports suggests that the prehospital mortality rate for penetrating subclavian trauma was approximately 75 per cent.

Conclusion: Approximately 25 per cent of subclavian artery injuries caused minimal initial symptoms but delayed complications prompted attendance for medical attention. The majority of patients who survived subclavian artery injury and attended for medical attention were haemodynamically stable on admission; selective arteriography provided valuable information in these patients. Supraclavicular and infraclavicular incisions avoided clavicular division and reduced the postoperative morbidity associated with distal subclavian artery injuries.

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Introduction

Trauma to the proximal axillary and subclavian vessels presents a surgical challenge particularly because the local anatomy prevents easy access and loss of control can result in rapid exsanguination. As these injuries are uncommon[1–3] most surgeons lack familiarity with their management and few are able to gain significant experience. In a major conflict, subclavian vascular trauma represented only 5 per cent of all vascular injuries[2] and in civilian series there was a similar incidence of between 3 and 9 per cent[1,4].

There are approximately four subclavian vascular injuries per month in Durban. Survivors represent approximately 3 per cent of all vascular injuries seen, as arterial trauma is common in South African practice[5]. Over the years the surgical approach to these injuries has changed, which prompted the present review of 20 years' experience.

Patients and methods

Details of all patients admitted under the care of the Metropolitan Vascular Unit are prospectively recorded on a computer database, allowing identification of patients who have sustained subclavian trauma. For the 20-year interval from 1977 until 1996 these records, and if necessary the case notes and radiographs, were reviewed for all patients documented with either subclavian or first-part axillary artery injury. Injuries to the proximal axillary artery were included because they are similar to third-part subclavian artery trauma and it can be difficult to distinguish between them anatomically. Brachiocephalic artery injuries were excluded. Two hundred and sixty patients were identified, of whom 29 were women; the mean age was 32 years. There were 55 right-sided subclavian vascular injuries.

To ascertain the true mortality rate associated with subclavian artery injury, forensic post-mortem reports for the 4 years 1993–1996 were investigated in a separate study. Only these records were available because before 1993 post-mortem reports were not retained on a computer database. Deaths from multiple vascular injuries were excluded as were those in which the arterial trauma was an additional injury.

Results

Mechanisms of injury

The majority of subclavian artery trauma resulted from stab wounds ($n = 214$, 82 per cent). Another 10 per cent followed low-velocity missile injuries. Shotgun wounds ($n = 8$) were graded separately owing to the frequent finding of multiple perforations and the severe associated soft tissue injury. A total of 35 injuries resulted from firearms and there were 11 (4 per cent) blunt trauma-related injuries.

Subclavian injuries were classified as either proximal, if the first or second parts of the artery were injured, or distal if the third part of the subclavian artery or proximal axillary artery was involved. One hundred and thirty-seven proximal subclavian and 123 distal subclavian injuries were identified.

In the majority of cases, from arteriographic and operative findings, it was possible to document the pathology of the arterial injury (*Table 1*).

Associated injuries

The commonest associated injuries were to adjacent local structures, namely the subclavian vein, brachial plexus, lung and clavicle (*Table 2*). There were 79 brachial plexus injuries, 56 of which were found at surgery to have sustained direct injury to the nerves; 20 were the result of compression of the nerves by a large false aneurysm. Primary brachial plexus repair was carried out if the patient was stable but not after gunshot wound or blunt trauma. There were three patients with avulsion-type injuries in association with traction trauma and two of these were noted to have an ipsilateral Horner's syndrome.

The five patients who sustained an additional arterial injury had shotgun trauma including damage to a brachial artery and two more distal axillary artery injuries. In four patients an additional stab wound necessitated laparotomy and one required a splenectomy. Two patients sustained an additional high-velocity gunshot injury to the lumbar spine which resulted in paraplegia.

Table 1 Pathology of subclavian artery injury in 260 patients

	No. of patients
Arteriovenous fistula	39 (15)
False aneurysm	75 (29)
Transection	72 (28)
Lateral perforation	32 (12)
Intimal injury – thrombosis	26 (10)
Uncertain	16 (6)

Values in parentheses are percentages

Table 2 Associated injuries to local structures in 260 patients with subclavian artery injury

	No. of patients
Venous injury	86 (33)
Brachial plexus injury	79 (30)
Haemothorax	26 (10)
Pneumothorax	14 (5)
Haemopneumothorax	7 (3)
Clavicular fracture	12 (5)
Other fracture	14 (5)
Additional arterial injury	5 (2)
Nerve injury	4 (2)
Tracheal injury	2 (1)
Thoracic duct injury	2 (1)

Values in parentheses are percentages

Clinical presentation

Fifty-nine patients (23 per cent) presented with a blood pressure of less than 70 mmHg and required resuscitation and surgery. Of these, 22 (37 per cent) had sustained gunshot wounds and the remaining 37 (63 per cent) had stab injuries.

Ninety-five patients (37 per cent) presented to hospital within the first 24 h of injury and were most likely to have an arterial bleed in combination with a weak or absent radial pulse. Patients with additional injuries such as pneumothorax or haemothorax tended to present early.

Thirty-nine patients (15 per cent) presented between 1 and 2 days following injury, and were more likely to have a large pulsatile haematoma. Often these patients were haemodynamically stable and had been referred from a peripheral hospital.

About one-quarter of patients, 67 (26 per cent), were seen more than 48 h following trauma. Patients in this group had minimal symptoms at the time of injury but developed complications that prompted their attendance. Delayed presentation was often characterized by brachial plexus symptoms or features of a traumatic arteriovenous fistula, such as arm swelling or venous distension. Included as late presenters were five patients attending after 1 week, ten within 4 weeks, and two patients presenting at 5 and 9 years following subclavian injury. Both of the latter patients had a well established arteriovenous fistula, and complained of arm swelling and venous distension with a marked mediastinal bruit.

Chest radiographic signs were predominantly mediastinal widening but a pleural cap was also documented. Other common signs noted at presentation are listed in *Table 3*.

Management

In the Metropolitan Vascular Unit haemodynamically stable patients with blunt or penetrating injury to the cervicomediastinum and those who improved sufficiently following initial resuscitation were managed by a policy of selective arch arteriography.

The decision regarding arteriography was made by the operating surgeon on criteria already established in the unit (*Fig. 1*). The surgeon accompanied the patient to the arteriography suite; if at any time the patient's condition deteriorated the investigation was terminated and the patient transferred directly to theatre.

Table 3 Signs of arterial injury in 260 patients with subclavian artery trauma

Sign of arterial injury	No. of patients
Pulse deficit	83 (32)
Arterial bleed	78 (30)
Chest radiography signs	42 (16)
Pulsating haematoma	37 (14)
Brachial plexus injury	37 (14)
Arm swelling	25 (10)
Arterial bruit	17 (7)
Multiple signs*	93 (36)

Values in parentheses are percentages. Some patients had more than one sign. *Combination of the above

One hundred and ninety-three patients had arch arteriography; only 19 patients did not proceed to surgery. In 17, this was because of late presentation with a complete brachial plexus paralysis and a viable upper limb. Arteriography showed subclavian thrombosis. The remaining two patients refused an operation.

Patients who presented in hypovolaemic shock that was unresponsive to resuscitation were transferred directly to the operating theatre and haemorrhage was controlled by gauze packs and manual compression until operative control was achieved.

Surgical access

Over the 20 years there has been a gradual evolution in the surgical approach. This obviously depended on the clinical presentation and site of the vascular injury, but in the early

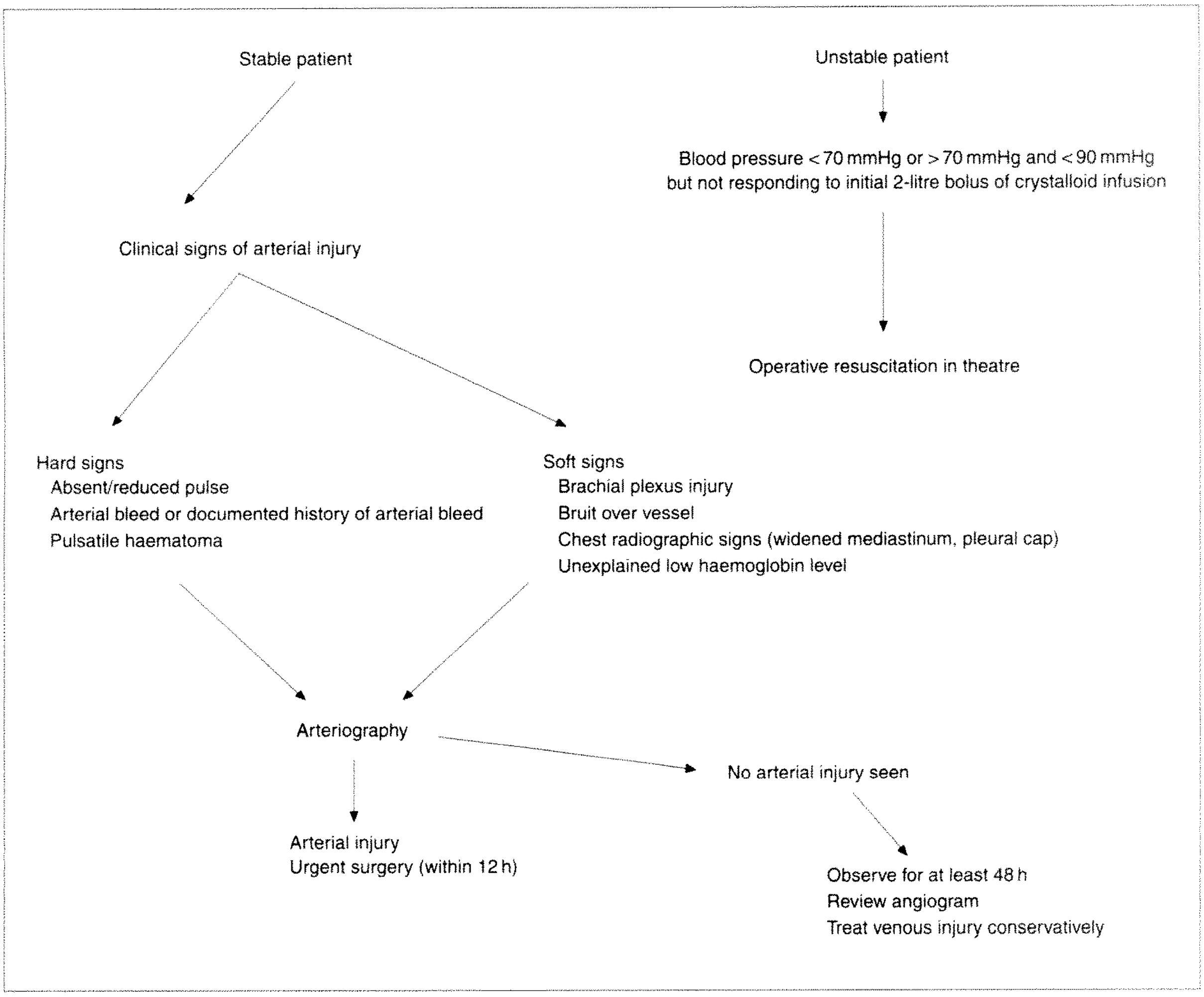
Stable patient
Unstable patient
Blood pressure < 70 mmHg or > 70 mmHg and < 90 mmHg
but not responding to initial 2-litre bolus of crystalloid infusion
Clinical signs of arterial injury
Operative resuscitation in theatre
Hard signs
Absent/reduced pulse
Arterial bleed or documented history of arterial bleed
Pulsatile haematoma
Soft signs
Brachial plexus injury
Bruit over vessel
Chest radiographic signs (widened mediastinum, pleural cap)
Unexplained low haemoglobin level
Arteriography
No arterial injury seen
Arterial injury
Urgent surgery (within 12 h)
Observe for at least 48 h
Review angiogram
Treat venous injury conservatively

Fig. 1 Management of penetrating cervicomediastinal trauma

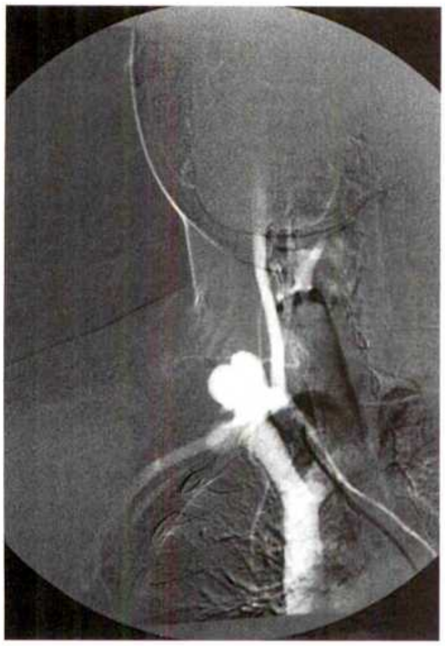

Fig. 2 Selective arteriogram at the bifurcation of the brachiocephalic artery. There is a traumatic false aneurysm at the origin of the right subclavian artery and an arteriovenous fistula is demonstrated with contrast flowing into the superior vena cava

period access to a proximal subclavian injury such as that shown in *Fig. 2* was by a total median sternotomy. More recently this has been achieved by limited sternotomy[6,7], although median sternotomy is still occasionally necessary to obtain good exposure, particularly in large men.

The approach to a distal subclavian or proximal axillary artery injury, as shown in *Fig. 3*, was originally via an incision parallel to, and crossing, the clavicle. The clavicle was divided at the midpoint[6,7]. Such was the morbidity of clavicular division that this incision was abandoned in favour of a medial supraclavicular and a lateral infraclavicular incision (*Fig. 4*). The frequency of use of the various methods of surgical approach is recorded in *Table 4*.

All patients were given perioperative intravenous antibiotics which were continued for 48 h.

Surgical repair technique

The commonest method of arterial repair was by autologous vein graft (95, 39 per cent) but both lateral suture (23, 10 per cent) and end-to-end anastomosis (88, 37 per cent) following adequate vessel debridement were also used frequently. A prosthetic graft was inserted on 24 occasions (10 per cent) and vein patch angioplasty was performed on six (3 per cent) patients.

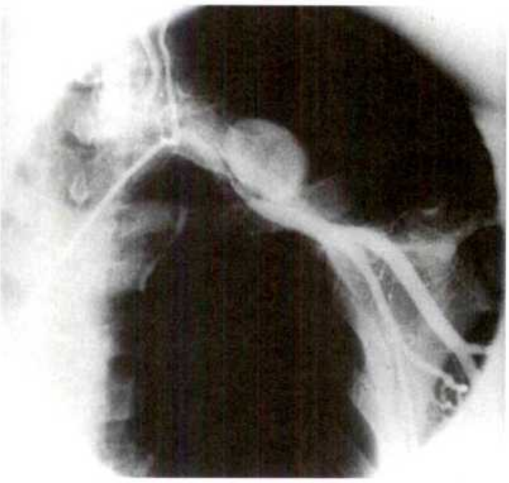

Fig. 3 Selective arteriogram of the left subclavian artery demonstrating a large traumatic false aneurysm of the proximal axillary artery

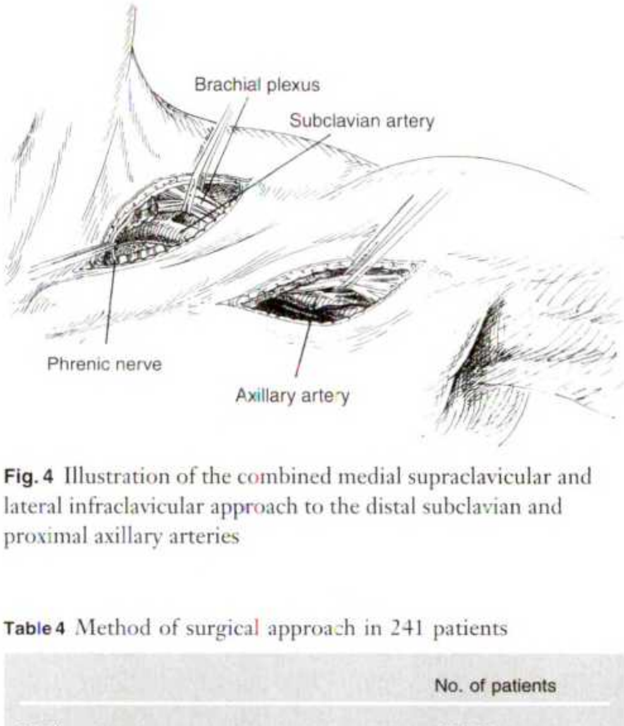

Fig. 4 Illustration of the combined medial supraclavicular and lateral infraclavicular approach to the distal subclavian and proximal axillary arteries

Table 4 Method of surgical approach in 241 patients

	No. of patients
Median sternotomy	44 (18)
Limited sternotomy	54 (22)
Supraclavicular incision only	55 (23)
Clavicular division	39 (16)
Supraclavicular and infraclavicular incisions	49 (20)

Values in parentheses are percentages

Subclavian artery ligation was carried out in five patients. In each of these there had been a delay in presentation and all had an obviously infected false aneurysm. There was no short-term morbidity reported following subclavian artery ligation. Associated subclavian venous injuries were common (33 per cent) and were repaired by lateral suture, if possible, but if necessary the subclavian vein was ligated. Patients with a venous component to the injury were managed where possible in the head-down position to reduce the risk of air embolism. Following subclavian vein ligation there was at most minimal oedema that responded to several days' arm elevation.

Postoperative complications

The most frequent complications were noted following clavicular division, before a change in the operative technique. There were 23 complications related to this approach with more than half of all divided clavicles causing postoperative problems. All of these complications were of sufficient severity to require referral to an orthopaedic surgeon. On five occasions as a result of infection the wound had broken down with exposure of the divided clavicle or suspected osteomyelitis, seven patients had malunion with a very poor cosmetic result and in the remainder the problem was either delayed union or pseudarthrosis.

There were 12 graft occlusions (10 per cent) that occurred in autologous vein grafts. Two patients with very early occlusion were returned to theatre for graft thrombectomy and revision of the anastomosis; in the remaining patients graft occlusion occurred later and, in the presence of a viable limb, no further intervention was undertaken. Some 79 patients had a brachial plexus injury and of these 14 (18 per cent) had a flail limb as a result of complete disruption of the brachial plexus.

As in other similar studies reported from South Africa[3,8], meaningful long-term follow-up was virtually impossible because, for socioeconomic reasons, most patients did not return for review. However, 16 patients attended the brachial plexus clinic in the hospital and were noted to have major neurological impairment.

There were 16 intraoperative deaths, eight following gunshot injury. These occurred in patients undergoing emergency surgery and were due to exsanguination. There were 14 postoperative deaths of which 11 occurred in patients who had undergone emergency surgery. These patients survived the surgical procedure but died from adult respiratory distress syndrome and multiple system organ failure as a result of massive preoperative and intraoperative blood transfusion.

Three patients died following planned surgery, all as a direct result of intraoperative blood loss. In one patient with proximal subclavian artery trauma, a supraclavicular approach proved inadequate to achieve control. In the other two patients with late presentation of a proximal subclavian arteriovenous fistula, there were severe technical difficulties, including inflammation and induration from the resolving haematoma and arterial pressurization of the venous system.

The combined intraoperative and postoperative mortality rate for the series was 12 per cent.

Post-mortem study

Analysis of Department of Forensic Pathology autopsy reports on violent deaths, for the years 1993–1996, revealed 135 deaths directly attributable to subclavian artery trauma. In these cases the reporting pathologist had documented exsanguination as the mode of death and there were no other major injuries. In total they contributed less than 1 per cent of all documented deaths due to violence in the 4 years.

Stab injuries of the subclavian artery were the most common cause, accounting for a total of 109 deaths (81 per cent). The majority (72) were the result of a knife wound to the left subclavian artery. Deaths from gunshot-related subclavian injuries were less frequent; 25 (19 per cent) were described in the 4-year interval.

According to Metropolitan Vascular Unit data, for the 4 years 1993–1996, there were 47 patients who survived surgery for subclavian vascular trauma. Therefore, from combined autopsy and vascular surgery data it was estimated that during these 4 years there were a total of 182 victims of subclavian artery trauma, of whom 135 (74 per cent) died as a result of the injury.

Discussion

In South Africa, over the 20-year interval, there has been a marked increase in the incidence of gunshot injuries with a corresponding decrease in stab wounds[8]. It was anticipated that post-mortem data would demonstrate significantly more gunshot than stab injuries[8]. However, these data also demonstrated a higher incidence of stab injuries compared with gunshot injuries. A high percentage of local patients are from a rural background and may lack the availability and sophistication of firearms usage seen in more urban-based populations.

The majority of patients (74 per cent) presented to a hospital within 48 h of their injury but a significant number (67, 26 per cent) did not attend or perhaps the arterial component of their injury was not appreciated when they first presented. Another study has shown that up to 32 per cent of patients with a significant vascular injury may have no specific clinical signs[9] and several authors have emphasized that many victims of subclavian trauma have clinically normal pulses[1,10]. Most patients with brachial plexus compression presented more than 2 days after injury and it was often the gradual onset of arm paralysis that prompted a patient to seek medical attention. This complication is usually a result of a large false aneurysm that compresses the trunks and cords of the brachial plexus[11,12] (*Fig. 3*). Despite surgical decompression the prognosis for this injury is poor; many patients have a residual flail limb and some eventually require above-elbow amputation[11,12]. The best results are achieved by early repair of the false aneurysm[12,13] which underscores one of the reasons for the policy of selective angiographic investigation.

The role of diagnostic arteriography is controversial. Policies vary from exploration on clinical diagnosis alone to routine arteriography for all stable patients with a cervicomediastinal wound[10,14,15]. The present policy of selective angiography based on clinical diagnosis has evolved over the 20-year interval[6,7] (*Fig. 1*). Arteriography not only reduces the risk of missing an occult vascular injury but also gives the surgeon the opportunity to tailor the surgical exposure more accurately to the site of the lesion and avoids the morbidity of an unnecessary sternotomy.

The surgical approach to distal subclavian injuries has also evolved significantly over the past 20 years. The frequency of clavicular complications noted in the early part of this study is much higher than that reported in other studies utilizing clavicular division[16,17]. However, in this unit, despite use of various methods of internal fixation, more than half of the divided clavicles caused subsequent problems. Many of the patients required urgent or emergency surgery and the surgeons involved had little orthopaedic experience. Other authorities avoid these complications by excision of part of the clavicle[8,18]; however, in patients who are employed as manual labourers, clavicular excision may prevent a return to normal activities. Combined medial supraclavicular and lateral infraclavicular incisions have resulted in good exposure (*Fig. 4*). If a subclavian artery bypass graft is necessary, an interposition graft can be tunnelled under the midpoint of the clavicle and anastomosed distally to the mid-axillary artery. The infraclavicular incision can also be extended laterally into the deltopectoral groove to facilitate further exposure of the axillary vessels.

Long saphenous vein grafting was the commonest method of repair although end-to-end anastomosis or lateral suture combined accounted for approximately 40 per cent. The preponderance of vein grafts may be the result of the policy of aggressive debridement and also a consequence of the technique that avoids clavicular division. Access to the distal subclavian artery may result in more grafts.

Ligation of subclavian vessels was reserved for cases in which delayed presentation had resulted in obvious sepsis. In patients with late graft occlusion the collateral network of the proximal upper limb is such that often only minimal symptoms result. In critically ill, haemodynamically unstable patients the subclavian artery should be ligated rather than prolonging an operation to carry out vein harvest and grafting[19].

The reported operative mortality rate for subclavian trauma ranges between 5 and 30 per cent[1,3,8,13] and in this series was 12 per cent. It has been suggested that the present operative technique in avoiding clavicular division may limit early control of distal subclavian injuries, but examination of these data shows no relationship between the site of the injury and the operative mortality rate.

Despite significant experience over 20 years the prognosis for victims of subclavian trauma remains poor. The combined data from Departments of Vascular Surgery and Forensic Pathology suggest that in the referral population of the Metropolitan Vascular Service there are approximately four victims of subclavian trauma per month of whom only one survives.

Acknowledgements

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Original article

Prospective study of safety, patient satisfaction and leg ulcer healing following saphenous and subfascial endoscopic perforator surgery

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Background: Subfascial endoscopic perforator surgery (SEPS) is a minimally invasive alternative to conventional techniques for incompetent calf perforators. Although SEPS has been performed for more than a decade, limited and insufficient data have been published regarding its safety, patient satisfaction and results.

Methods: A prospective follow-up was undertaken of consecutive SEPS operations on 149 legs, performed in 138 patients: 67 legs with ulceration, 34 with skin changes and 48 with varicose veins. Conventional saphenous vein surgery was performed, when indicated, together with the SEPS procedure. Follow-up was performed after 1 week and later by postal questionnaire to assess long-term morbidity, late complications and patient satisfaction. Patients with ulcers were followed continuously.

Results: Most operations ($n = 107$) were performed as day-case surgery. Combined saphenous vein surgery was performed in 89 per cent. No serious complications occurred: wound infection in 7 per cent; severe postoperative pain in 9 per cent; delayed wound healing in 15 per cent. After a median follow-up of 7 (1–31) months, 91 per cent of patients were satisfied. After a median of 32 (14–57) months, ulcer healing had occurred in 30 of 36 patients with open ulceration at the time of operation.

Conclusions: SEPS is a safe procedure, suitable for day-case surgery. Patients are generally satisfied with the outcome and the results of leg ulcer healing are promising.

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Introduction

Subfascial endoscopic perforator surgery (SEPS) has evolved as a convenient way of dealing with incompetent perforating veins in the lower leg. Although the technique was developed in the 1980s[1], it did not gain acceptance until after the introduction of video-assisted laparoscopic surgery[2]. One reason for the slow acceptance was the lessons learned from the uncontrolled introduction of laparoscopic cholecystectomy[3]. Furthermore, the introduction of SEPS started a debate regarding the role of incompetent perforators in the development of chronic venous insufficiency (CVI)[4]. The scientific documentation regarding SEPS is still limited and based mainly on results from a few retrospective studies[1,5–8]. There have been only four small prospective studies[9–12] and only one randomized study[13]. Most of these reports give insufficient data to judge the outcome and morbidity associated with SEPS.

The aims of this study were to establish the morbidity, patient satisfaction and long-term results of SEPS with regard to healing and recurrence of venous leg ulcers.

Patients and methods

Between March 1993 and June 1997, 149 operations were performed by, or under the supervision of, the author. Operations were carried out on 138 patients: 82 women (87 legs) and 56 men (62 legs) of median age 58 (range 25–86) years.

Preoperative assessment

The preoperative assessment included history, clinical examination and bidirectional Doppler ultrasonography. The 46 patients operated on before 1995 had no additional assessments. Since 1995 colour-coded duplex Doppler ultrasonography (Acuson 128XP; Acuson, Mountain View, California, USA) has been used to locate perforators and to verify venous incompetence in patients with leg ulcers, severe skin changes and recurrent varicose veins. Among patients with symptomatic varicose veins, the SEPS procedure was used as a diagnostic tool to locate perforators that, based on clinical examination, were suspected of being incompetent[14].

Based on preoperative examination, venous insufficiency was classified according to Widmer *et al.*[15] and recommendations from the Society for Vascular Surgery and the International Society for Cardiovascular Surgery[16]. The clinical classification was updated when the CEAP (Clinical Etiological Anatomical Pathophysiological) classification appeared[17,18]. Only limbs with CVI C3 or worse were considered for SEPS with or without combined superficial venous surgery. All patients with ulcers had been treated with compression bandaging before operation.

Legs with incompetence in the popliteal vein below the knee were considered to have a significant deep venous insufficiency (DVI). All other legs were considered to have predominant superficial venous insufficiency (SVI) and/or perforator venous insufficiency. Patients with ulcers and DVI were offered surgery only if the ulcer did not heal with conventional compression treatment. A chronic venous leg ulcer was defined as any wound below the knee, with a predominant Doppler ultrasonographically verified venous reflux and ankle : brachial pressure index of 0·8 or more, that had been present unhealed for more than 6 weeks.

Surgical procedure

Informed consent was received from all patients. Prophylactic antibiotics and thromboembolic prophylactics were given selectively. A Storz 10-mm endoscope for perforating vein ligation (Karl Storz, Tüttlingen, Germany) and video-camera equipment were used. SEPS was performed in a bloodless field, created by a roll-on tourniquet (Boazul, Lidköping, Sweden). The basic SEPS technique has been described by others[1,7]. The distal part of the deep compartment fascia was divided by sharp dissection to visualize the lower Cockett perforators[19], and lateral perforators were dealt with by means of a contralateral incision. High ligation and stripping were generally used for additional SVI.

Follow-up

Specially trained nurses saw all patients 7–10 days after operation at the outpatient clinic. Early complications were noted. Patients without leg ulcers received a compression stocking (class 1), which they were encouraged to use for 1 month. Patients with open ulcers were treated with a zinc paste stocking bandage (Salvstrumpa; Smith & Nephew, Mölndal, Sweden). The surgeon saw patients with leg ulcers after 3–4 months and thereafter until healing. Only patients with DVI were provided with prophylactic compression hosiery after leg ulcer healing.

To assess long-term complications, patient satisfaction and leg ulcer healing, a postal questionnaire was sent to all patients. Long-term healing and recurrent ulceration among patients with open ulcers at the time of operation were monitored by repeated telephone interview with patients, relatives or carers. The results were analysed overall as well as in subgroups of the different clinical classes of CVI (C3–C6), and were based on consecutive patients (operated limbs).

Results

A total of 149 SEPS procedures were attempted, of which only one had to be aborted. Lateral perforators were dealt with in 13 limbs. Demographic data, deep vein involvement and resulting sick leave are shown in *Table 1*. A majority of

Table 1 Demographic data for patients undergoing subfascial endoscopic perforator surgery

	All legs (C3–C6)	Varicose veins (C3)	Skin changes (C4)	Leg ulcer, healed or open (C5–C6)
No. of legs	149	48	34	67
Median (range) age (years)	58 (25–86)	50 (25–83)	57 (37–78)	66 (38–86)
Sex ratio (F : M)	87 : 62	29 : 19	19 : 15	39 : 28
Retired*	66 (44)	12 (25)	15 (44)	39 (58)
Bilateral operation	11	3	1	7
DVI*	11 (7)	0 (0)	1 (3)	10 (15)
Median (range) time off work (days)	14 (0–37)	14 (0–27)	17 (0–24)	14 (0–37)

*Values in parentheses are percentages. DVI, deep venous insufficiency

Table 2 Type and duration of operation performed

	All legs (*n*=149)	Varicose veins (*n*=48)	Skin changes (*n*=34)	Leg ulcer, healed or open (*n*=67)
Previous venous surgery*	49 (33)	15 (31)	6 (18)	28 (42)
Day-case surgery*	107 (72)	46 (96)	31 (91)	30 (45)
Median (range) operating time (min)	80 (45–145)	80 (55–145)	77 (55–140)	90 (45–145)
Median (range) tourniquet time (min)	55 (10–95)	50 (30–80)	55 (35–70)	60 (10–95)
Median (range) no. of perforators ligated	4 (0–8)	3 (0–6)	4 (1–7)	5 (0–8)
Type of surgery performed*				
Long saphenous + SEPS	97 (65)	38 (79)	21 (62)	38 (57)
Short saphenous + SEPS	29 (19)	5 (10)	9 (26)	15 (22)
Long and short saphenous + SEPS	6 (4)	1 (2)	2 (6)	3 (4)
SEPS only	17 (11)	4 (8)	2 (6)	11 (16)

*Values in parentheses are percentages. SEPS, subfascial endoscopic perforator surgery

Table 3 Postoperative morbidity, complications and complaints following subfascial endoscopic perforator surgery

	All legs (*n*=149)	Varicose veins (*n*=48)	Skin changes (*n*=34)	Leg ulcer, healed or open (*n*=67)
Stripping haematoma, thigh	15 (10)	6 (13)	5 (15)	4 (6)
Skin burn*	1 (1)	0 (0)	0 (0)	1 (1)
Haematoma, calf	5 (3)	2 (4)	1 (3)	2 (3)
Severe swelling	9 (6)	5 (10)	2 (6)	2 (3)
Severe pain	13 (9)	7 (15)	4 (12)	2 (3)
Sensory disturbance	9 (6)	3 (6)	2 (6)	4 (6)
Thrombophlebitis	13 (9)	6 (13)	2 (6)	5 (7)
Wound infection	11 (7)	1 (2)†	0 (0)	10 (15)
Delayed wound healing	22 (15)	3 (6)	0 (0)	19 (28)
Initial walking disturbance	44 (30)	16 (33)	10 (29)	18 (27)

Values in parentheses are percentages. *Induced by insufficient cooling of the rubber wedge for the tourniquet; †infected wound in the groin

procedures, 101 (68 per cent) of 149, were performed in limbs with skin changes or ulcers. Data regarding the surgery performed are shown in *Table 2*.

Complications

No serious complications occurred. Apart from complaints regarding initial walking disturbance (30 per cent), one or more minor complications were noted in 46 limbs (31 per cent). Details regarding postoperative morbidity, complications and complaints are shown in *Table 3*. The most common complications were delayed wound healing and wound infections. These complications appeared, with few exceptions, among patients with leg ulcers (healed or open). Severe pain within the first week after surgery was noted in 9 per cent of patients, more frequently amongst those with varicose veins. None developed persisting pain.

Patient satisfaction

The actual operation was well tolerated; only 12 per cent found it somewhat disturbing and one patient found it very troublesome. In the postoperative period 42 per cent used no analgesics, 33 per cent used occasional tablets and 16 per cent used regular medication for a couple of days (7 per cent for 1 week or more). At a median of 7 (range 1–31) months after operation, more than 80 per cent reported that they were cured or improved (*Fig. 1*). The majority considered the cosmetic result satisfactory (*Table 4*). Overall, 91 per cent were satisfied with the outcome. Most patients stated that they would prefer a SEPS procedure if they had to

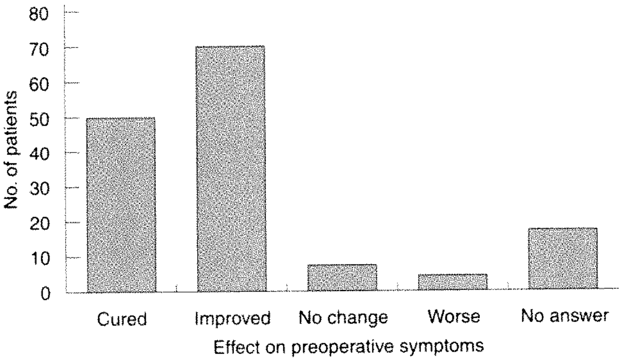

Fig. 1 Patient opinion regarding symptomatic relief from subfascial endoscopic perforator surgery

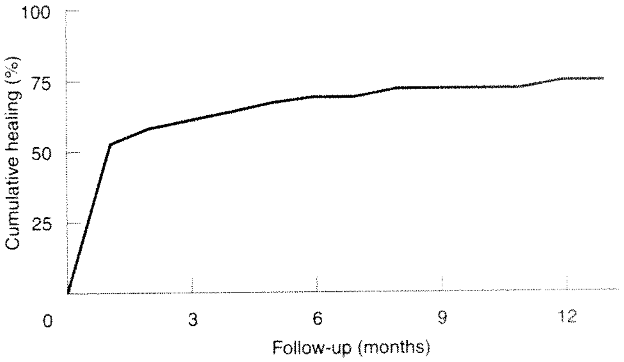

Fig. 2 Cumulative leg ulcer healing 1 year after subfascial endoscopic perforator surgery

Table 4 Patient opinion regarding the cosmetic result following subfascial endoscopic perforator surgery

	All legs (*n* = 149)	Varicose veins (*n* = 48)	Skin changes (*n* = 34)	Leg ulcer, healed or open (*n* = 67)
Excellent	67 (45)	20 (42)	16 (47)	31 (46)
Fairly good	44 (30)	19 (40)	12 (35)	13 (19)
Good	18 (12)	5 (10)	2 (6)	11 (16)
Not so good	14 (9)	4 (8)	2 (6)	8 (12)
Bad	1 (1)	0 (0)	1 (3)	0 (0)
No answer	5 (3)	0 (0)	1 (3)	4 (6)

Values in parentheses are percentages

undergo surgery again; 79 per cent answered 'yes – absolutely' and 17 per cent 'yes – maybe'.

Long-term follow-up of leg ulcers

After a median follow-up of 32 (range 14–57) months, 30 of 36 ulcers were healed (two patients died with healed ulcers). In most limbs healing progressed rapidly (*Fig. 2*). More than half (19 of 36) had healed within 1 month of surgery. The 12-week healing rate was 22 of 36, and after 1 year 27 of 36 had healed. Altogether the original ulcer had healed in 32 patients, but three experienced recurrences, of which two remained unhealed. The preoperative and postoperative ulcer history, for all patients, is shown in *Fig. 3*. Two of the six patients with DVI had open ulcers at the end of follow-up, compared with four of 30 with SVI.

Discussion

This study is the largest prospective study of SEPS yet published and the first to analyse subgroups of patients with disabling CVI (C3–C6). Some previous reports have focused on patients with severe CVI, i.e. skin changes or ulcers (C4–C6)[1,8,9,11,13], whilst others have performed SEPS mainly among patients with regular varicose veins (C2 and C3)[5–7,12].

In accordance with previous reports[20,21] the number of divided perforators in this study increased with severity of venous disease (*Table 2*), and more perforators were identified during SEPS than were detected on the preoperative scan[22,23]. It appears that size of perforators is related to the likelihood of being incompetent, and most large perforators (4 mm or more) may be expected to be pathological[21] and merit ligation. One-third of incompetent perforators are, however, of a smaller size[21]. When performing SEPS, perforators greater than 2 mm should be ligated, since incompetent lower leg perforators appear to be a common source for varicose vein recurrence[24] and contribute to non-healing venous ulcers[11,23,25].

Whether or not perforators should be dealt with at all remains a controversial question[4,26], especially regarding patients without skin changes. Perforator ligation alone has, however, been claimed as an effective treatment for non-healing venous ulcers[9,25]. The present results support this claim since SEPS was the only operation performed in 16 per cent of limbs with leg ulcers, all of which healed.

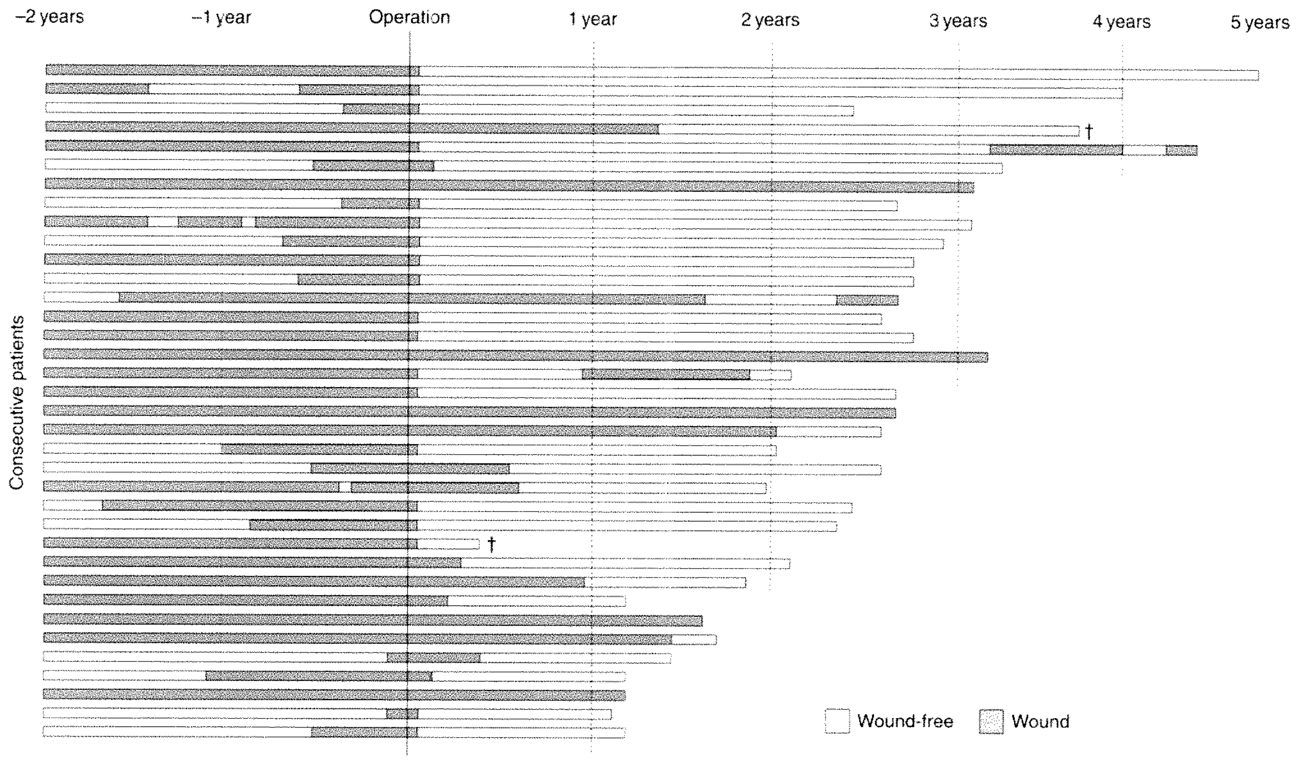

Fig. 3 Preoperative and postoperative leg ulcer history at a median follow-up of 30 months for patients with unhealed ulcers who underwent subfascial endoscopic perforator surgery. †Patient dead

Furthermore it has been shown that reflux in the local area around the ulcer is of importance[27], that perforators play a role in the development of leg ulcers[11,13,25] and that saphenous surgery alone cannot cure all patients[28].

As this was a prospective study, with one of the main aims to look at the morbidity associated with SEPS, every possible complaint was recorded. In keeping with other reports[11] some complaints or minor complications occurred in about one-third of cases. Contrary to the findings of others[7,8,11], delayed healing of the incision made for SEPS was a fairly common occurrence. Explanations for this may be a higher rate of detection, wider criteria and insufficient postoperative compression treatment. Most patients, however, considered delayed healing a minor problem.

The combination of SEPS and saphenous surgery had a dramatic effect on leg ulcer healing. Despite a preoperative median duration of current ulceration of 2 years, 53 per cent of ulcers were healed within 1 month after operation (*Fig. 2*). Over a median 32 months' follow-up, three of 32 ulcers recurred, of which two remained unhealed at the end of the study. These results are promising and better than the recently published results from the North American Subfascial Endoscopic Perforator Surgery Registry (28 per cent recurrence after 2 years)[29]. The reason for the high recurrence rate in the latter study was probably the fact that the majority of patients had DVI.

SEPS with or without combined superficial venous surgery is an effective way of dealing with non-healing or slowly healing venous leg ulcers, especially in legs without DVI. Whether treatment with superficial venous surgery alone[30,31] can match these results has, however, to be decided through a randomized controlled study. This study has shown that SEPS in combination with superficial venous surgery is safe and feasible among patients with varying degrees of venous insufficiency. Patient satisfaction was high and the objective results of long-term healing of venous leg ulcers are promising.

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Autonomic nerve plexus involvement and prognosis in patients with rectal cancer

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Background: A detailed knowledge of the fundamental basis for cancer involvement of the autonomic nerve plexus and the outcome of patients with such cancer foci is important when considering nerve-preserving surgery for rectal cancer.

Methods: Extrarectal autonomic nerve plexuses were obtained from 61 patients with advanced rectal cancer who were undergoing extended resection of the rectum with the associated nervous system. The specimens were sectioned totally so that any indirect cancer involvement of the extrarectal autonomic nerves and/or the surrounding tissue could be detected.

Results: Autonomic nerve plexus involvement was observed in nine patients: none of 25 with Dukes A/B, six of 28 with Dukes C and three of eight with Dukes 'D' lesions. Five of 26 patients with nodal involvement in the pararectal area had such foci, and four of eight patients with nodal involvement further from the primary tumour. Furthermore, of the nine patients with nerve plexus involvement, seven had extranodal cancer deposits in the mesorectum. The 3-year survival rate of patients with nerve plexus involvement was 33 per cent, while it was 83 per cent in those without such disease.

Conclusion: Nerve plexus involvement was observed in direct proportion to the extent of cancer spread to the mesorectum, and the prognosis of patients with such disease was unfavourable. Further investigation is needed to better identify those patients who would clearly benefit from an *en bloc* resection of the autonomic nerves.

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Introduction

Compared with colon cancer, the distinguishing clinical characteristics of rectal cancer are a high incidence of local recurrence and autonomic nerve dysfunction after surgery. In recent years, the possibility of nerve preservation has attracted attention owing to the severe degree of functional disturbance caused by radical surgery[1–7]. Issues related to nerve dissection, however, have not been investigated sufficiently in relation to the mode of discontinuous cancer spread to the extrarectal nerve plexus[8–10]. In addition, the survival benefit associated with the dissection of autonomic nerves and the cancer foci around them, which can be a major source of local tumour recurrence in nerve preservation cases, has not been assessed.

In this study, cancer involvement of the autonomic nerve plexus outside the rectum was investigated and the clinicopathological features of patients with this type of cancer focus were analysed. Furthermore, it was possible to clarify the prognostic outcome of patients with such foci who underwent extended resection of the rectum with autonomic nerve plexuses.

Patients and methods

Sixty-one patients who underwent an extended resection of the rectum and associated autonomic nerves (superior hypogastric plexus, bilateral hypogastric nerves and bilateral inferior hypogastric plexuses) for advanced rectal adenocarcinoma at the Department of Surgery I of the National Defense Medical College Hospital from 1993 to 1996 were included in the study. During this period, an extended resection of the rectum with autonomic nerve plexuses was performed as a standard procedure, when either lymph node metastasis or tumour penetration through the muscular layer of the rectal wall was suspected based on both preoperative and intraoperative examinations. The patients included 41 men and 20 women, with a

Table 1 Clinicopathological background of patients undergoing extended resection of the rectum including removal of autonomic nerve plexuses

	No. of patients
Tumour location	
Above the peritoneal reflection	23
Below the peritoneal reflection	38
Depth of invasion	
pT2	7
pT3	50
pT4	4
Tumour differentiation	
Well differentiated	15
Moderately differentiated	43
Mucinous carcinoma	3
Lymphovascular invasion	
None–mild	31
Moderate–significant	30
Venous invasion	
None–mild	26
Moderate–significant	35
Nodal involvement	
None	27
Pararectal nodes	26
Nodes around superior rectal artery	8
Extranodal cancer spread in mesorectum	
Absent	42
Present	19
Dukes stage	
A	5
B	20
C	28
'D'	8

mean age of 61 (range 41–83) years. Forty patients underwent anterior resection, 20 underwent abdominoperineal resection and one had a total pelvic exenteration. The clinicopathological background of the patients is given in *Table 1*. Any patient with a macroscopically bulky tumour involving the pelvic plexus or hypogastric nerve was excluded from this study.

Immediately after resection of the surgical specimen, the autonomic nerves running along the rectum were serially excised by the same technique as that used for nerve preservation, and were then stretched and pinned to a cork board. The nerve specimens were sliced at 4-mm intervals after formalin fixation for at least 48 h (*Fig. 1*). The sections were stained with haematoxylin and eosin, and all specimens were inspected for the presence of extrarectal nerve plexus involvement, which was defined as cancer involving either the nerve fascicles or the surrounding tissue that would normally remain *in situ* in a nerve-preserving procedure.

For the prognostic analysis, 53 patients who underwent potentially curative surgery were investigated. The follow-up period in this group ranged from 27 to 55 (mean 37) months.

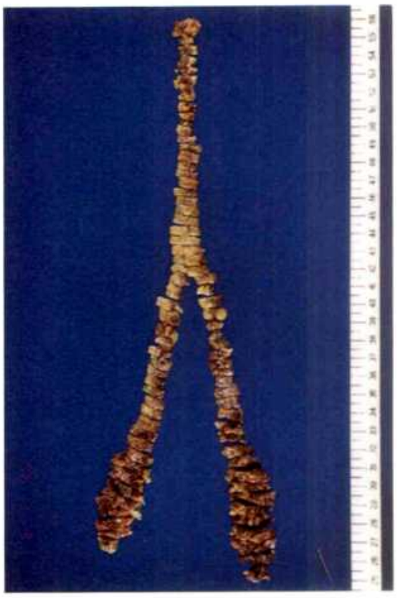


Fig. 1 Resected and fixed specimen of the autonomic nervous system outside the rectum, sliced at 4-mm intervals

Statistical analysis was carried out using the χ^2 test or Fisher's exact test and the unpaired *t* test as appropriate. Survival curves were created using the Kaplan–Meier method; the log rank test and univariate analysis using the Cox proportional hazard model were performed for comparisons.

Results

Autonomic nerve plexus involvement was found in nine (15 per cent) of 61 patients, and the tumour foci ranged between 50 µm and 4 mm in diameter. Plexus involvement was observed as perineural invasion (two patients) (*Fig. 2a*), tumour deposits in surrounding tissue close to the autonomic nerves (seven) (*Fig. 2b*), or involvement of attached tiny lymph nodes (two).

Tumour involvement of the superior hypogastric plexus was observed in two patients, while the hypogastric nerve was involved in two and the inferior hypogastric plexus in six. All patients with involvement of the inferior hypogastric plexus had a primary tumour with a lower border located below the peritoneal reflection.

Features of patients with nerve plexus involvement

No relationship was observed between nerve plexus involvement and the maximum tumour diameter, while the extent of lymphatic and venous vessel invasion of the primary tumour was significantly related to the existence of such foci (*Table 2*). Nerve plexus involvement was not

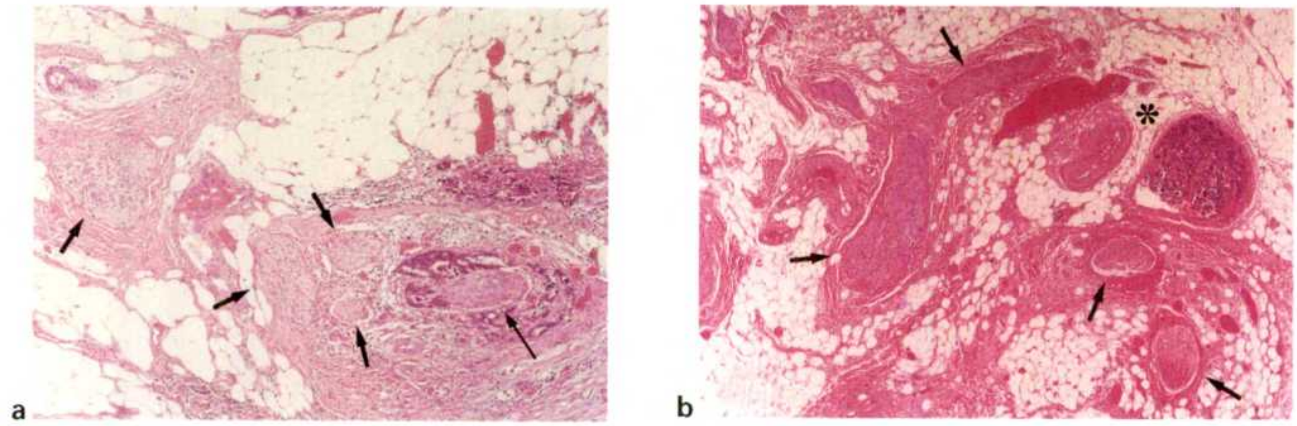


Fig. 2 Histological findings of nerve plexus involvement.
a Perineural invasion (arrows represent nerve fascicles).
b Tumour deposit (*) in tissue around the nerve fascicles (arrows).
(Haematoxylin and eosin stain, original magnification × 25)

Table 2 Relationship between cancer involvement of the autonomic nerve plexus and various clinicopathological characteristics

	Nerve plexus involvement		
	No	Yes	P‡
Lymphovascular invasion			0·013
None–mild	30	1	
Moderate–significant	22	8	
Venous invasion			0·007
None–mild	26	0	
Moderate–significant	26	9	
Nodal involvement			
None	27	0	
Pararectal nodes	21	5	0·023*
Nodes around superior rectal artery	4	4	0·001*
Extranodal cancer spread in mesorectum			0·003
Absent	40	2	
Present	12	7	
Dukes stage			
A	5	0	
B	20	0	
C	22	6	0·024†
'D'	5	3	0·01†

**Versus* node negative; †*versus* Dukes A + B. ‡χ^2 test

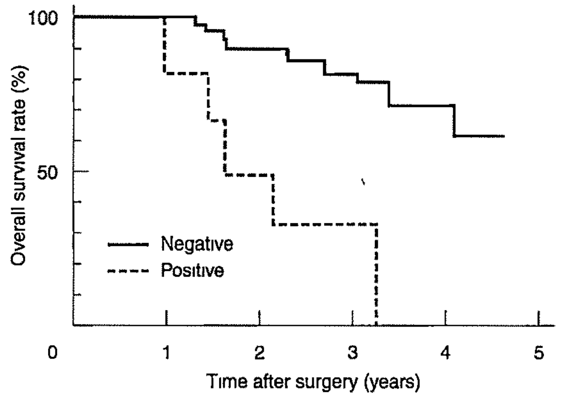
observed in patients whose primary tumour was confined to the rectal muscular layer or in patients with no nodal involvement. Five of 26 patients with pararectal nodal involvement also had nerve plexus involvement, compared with four of eight patients with nodal involvement around the superior rectal artery. Extranodal cancer foci discontinuous with the primary tumour in the mesorectum were observed in seven of nine patients with nerve plexus involvement. No patient with Dukes A or B disease had nerve plexus involvement, whereas six of 28 with Dukes C and three of eight with Dukes 'D' lesions had such disease.

Outcome of patients with nerve plexus involvement

Four of six patients with nerve plexus involvement who underwent potentially curative surgery could be cured locoregionally. Nevertheless, the overall survival curve of these patients was significantly worse than that of those without such foci because of systemic recurrence ($P < 0{\cdot}001$) (*Fig. 3*). Based on univariate analysis using the Cox proportional hazard model, mortality risk increased by 7·7 (95 per cent confidence interval 2·5–23·8) times in patients with nerve plexus involvement. The 3-year survival rate was 33 per cent for patients with nerve plexus involvement and 83 per cent for those without such involvement. All recurrences in patients with nerve plexus involvement occurred within 1 year.

Discussion

Urinary and sexual dysfunction, caused by the intentional or accidental sacrifice of the autonomic nerves supplying the genitourinary organs, is one of the most serious drawbacks of surgery for rectal cancer. Enker[11] has reported a good maintenance of male sexual potency using an autonomic nerve-preserving pelvic side wall dissection, and Heald *et al.*[1,5] have reported a very low local recurrence rate at 5 years after curative anterior resection with mesorectal excision within the plane of the inferior hypogastric plexus, which was carefully preserved. Furthermore, Hojo *et al.*[2]



No at risk					
Negative	47	47	43	19	7
Positive	6	5	3	1	0

Fig. 3 Comparison of the survival curves of patients with rectal cancer who underwent curative surgery, based on extrarectal autonomic nerve involvement. Positive, patients with autonomic nerve plexus involvement; negative, patients without nerve plexus involvement. $P < 0{\cdot}001$ (log rank test)

and Maas *et al.*[7] have obtained good functional results after nerve-preserving radical rectal resection in Japanese and Dutch patients.

On the other hand, the cancer foci remaining in the operative field after such nerve-preserving operations can result in local recurrence. It is therefore important to recognize clearly the risk of recurrence for each patient undergoing nerve-preserving surgery. The incidence of autonomic nerve plexus involvement by rectal cancer was 15 per cent in this series, which is comparable with previously reported figures (10–15 per cent)[8–10]. It is impossible to control local recurrence in patients with this level of involvement using total mesorectal excision[1,5,12,13]. It was also revealed that the fatty tissue around the nerve fascicles is clinically important in the cancer spread field. Total excision of the tissue around the nerve is thought to be impractical, and this procedure might also cause devascularization and traction injury to the preserved nerves[4,11]. There is therefore some possibility that tiny cancer deposits around the nerve fascicles represent the origin of local recurrence after nerve-preserving resection.

Patients who are most suitable for nerve-preserving procedures have not yet been clearly identified. Based on the small foci in the nerve plexus revealed in this study, foci that could not be detected directly using standard preoperative imaging methods or by intraoperative observation, some indirect indicators are thought to be necessary. In this series, all patients with nerve plexus involvement had tumours that penetrated the rectal muscle layer. In addition, all patients with such foci had regional lymph node involvement, a finding which supports the report by Sugihara *et al.*[4] who have suggested that enlarged perirectal lymph nodes could be used as one of the indicators for deciding whether or not to perform non-nerve-preserving procedures.

There are still few detailed investigations regarding the outcome of patients who have cancer involvement of the autonomic nerves outside the rectum. Based on the present findings, patients with regional nodal involvement or discontinuous extranodal cancer foci in the mesorectum, which reflect an aggressive tumour biology[14,15], should be treated by non-nerve-preserving surgery on the assumption that curative treatment cannot be achieved by total nerve-preserving surgery. However, in this series, a favourable prognosis for patients with nerve plexus involvement could not be obtained by extended resection of the rectum with the autonomic nerve plexus. Four of six such patients could be controlled locoregionally by performing an extended resection of the rectum with the associated nervous system; all but one of these patients, however, showed a cancer relapse within a short period after curative surgery, with the relapse usually consisting of distant metastasis to the liver. Although the study size should be taken into account when interpreting the results, based on the above findings, an extended rectal resection including the removal of the whole nerve plexus remains questionable as the standard procedure for all patients with advanced rectal cancer. Further investigations are needed to better identify patients with nerve plexus involvement who would clearly benefit from *en bloc* resection of the autonomic nerves.

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Original article

Prospective audit following the introduction of short-course preoperative radiotherapy for rectal cancer

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Background: The value of introducing a short course of preoperative radiotherapy before operation for rectal cancer is still subject to debate.

Methods: One hundred consecutive patients, of mean age 68 (range 29–87) years undergoing preoperative radiotherapy for rectal cancer between January 1997 and December 1998 at two radiotherapy centres were audited prospectively.

Results: The time from referral to radiotherapy was 33 (11–74) days and from radiotherapy to operation 5 (1–42) days. There was a higher than expected anastomotic leak rate (15 per cent) and perineal wound infection rate (18 per cent). Patients waiting more than 7 days were more likely to suffer perineal wound breakdown: 15 per cent ($n = 39$) *versus* 30 per cent ($n = 10$).

Conclusion: The high anastomotic leak and perineal wound infection rates suggest that the introduction of preoperative radiotherapy combined with total mesorectal excision should be audited carefully or performed as part of the CRO7 trial.

Presented to the Association of Coloproctology of Great Britain and Ireland in St Helier, Jersey, June 1998

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Introduction

The value of adding radiotherapy to surgery in the treatment of patients with rectal cancer has long been debated. The benefit of a lower recurrence rate has to be balanced against increased morbidity and mortality rates. The impressive results of the Swedish Rectal Cancer study group[1], with acceptable perioperative morbidity and mortality rates[2], have led many surgeons to adopt the Uppsala regimen in the hope of reducing local recurrence and improving long-term survival. Experience following the introduction of this regimen by some surgeons in North Trent has been audited prospectively.

Patients and methods

One hundred consecutive patients, of mean age 68 (range 29–87) years, undergoing preoperative radiotherapy for rectal cancer between January 1997 and December 1998 at two radiotherapy centres were audited prospectively. Data were collected by completion of a comprehensive and preagreed data set. All patients had a histologically proven adenocarcinoma within 15 cm of the anal verge which was considered to be resectable by the referring surgeon.

Irradiation technique

Radiotherapy was delivered at one of two centres (Sheffield and Lincoln). Following assessment by computed tomography, four ports of radiotherapy were used to deliver 25 Gy in five fractions over 5 consecutive days. The target volume included the upper limit of S1 as the superior border, 2 cm distal to the inferior margin of the palpable tumour as the inferior border or if the operation was to be abdominoperineal resection to include the perineum. The anterior limit was 1·5 cm anterior to the defined cancer. The posterior limit was the posterior border of the sacrum and the lateral margins 1·5 cm lateral to the pelvic side walls.

With a view to providing this service in the National Health Service, the time taken from surgical referral to beginning radiotherapy as well as the time from radiotherapy to surgery were monitored. To be acceptable, radiotherapy should commence as soon as possible after referral (within 4 weeks), with surgery within 1 week of completion of radiotherapy.

Surgery and histopathology

Referrals were from both teaching hospitals and district general hospitals, and were representative of the service available in the region. All participating surgeons had a declared and demonstrable interest in colorectal surgery. All surgeons reported performing total mesorectal excision as described by Heald *et al.*[3] and had previously attended a course to learn this technique. Resection specimens were reported by a local pathologist according to the criteria defined by the Royal College of Surgeons[4].

Results

For comparison and where appropriate the data are presented alongside the published Uppsala results[2] (*Tables 1–4*).

There were 80 men with a median age of 68 (range 29–83) years and 20 women of median age 67 (range 47–87) years, which is similar to that reported in the Uppsala papers[1,2]. Eight patients in the North Trent series were over 80 years of age, a group that was excluded from radiotherapy in the Swedish trial.

The operations performed are listed in *Table 1* and the Dukes classification of resected tumours is shown in *Table 2*.

Radiotherapy

All patients received the planned course of radiotherapy which was started on a Monday and delivered over 5 consecutive days.

The median time from referral to commencing radiotherapy in North Trent was 33 (range 11–74) days; that from radiotherapy to surgery was 5 (range 1–42) days, compared with 7 (range 3 to more than 15) days in the Uppsala study.

Table 1 Operations performed

Operation	Uppsala (n=553)	North Trent (n=100)
Anterior resection	243 (43·9)	46 (46)
Abdominoperineal resection	304 (55·0)	46 (46)
Hartmann's	5 (0·9)	5 (5)
Panproctocolectomy	1 (0·2)	3 (3)

Values in parentheses are percentages. There were no significant differences between the Uppsala and North Trent series

Table 2 Dukes classification of resected tumours

Dukes stage	Uppsala (n=553)	North Trent (n=100)	P^*
A	181 (32·7)	11 (11)	<0·001
B	195 (35·3)	45 (45)	
C	177 (32·0)	44 (44)	

Values in parentheses are percentages $^*\chi^2$ test

Table 3 Major complications

Complication	Uppsala	North Trent
Anastomotic leak	26 of 243 (10·7)	7 of 46 (15)
Perineal wound infection	63 of 304 (20·7)	9 of 49 (18)
Wound infection	25 of 553 (4·5)	8 of 100 (8)

Values in parentheses are percentages. There were no significant differences between the Uppsala and North Trent series

Table 4 Hospital stay according to surgical procedure

Operation	Uppsala	North Trent
Anterior resection (days)	19 (7–79)	13 (7–57)
Abdominoperineal resection (days)	25 (8–121)	15 (8–104)
Hartmann's (days)	29 (10–42)	16 (10–20)
Panproctocolectomy (days)	51 (n=1)	8–18 (n=3)

Values are median (range)

Mortality and morbidity rates

The hospital and 30-day mortality rate in the North Trent series was 3 per cent compared with hospital and 30-day mortality rates of 4 and 2 per cent respectively in the Uppsala study.

Nineteen of 46 patients undergoing an anterior resection in North Trent had a documented complication compared with 34 per cent in the Uppsala series; half of the patients undergoing abdominoperineal resection had a documented complication in both series. The major complications of wound infection, anastomotic leak and perineal wound infection are specifically reported in *Table 3*. The perineal wound infection rate was six of 39 if the operation was performed within less than 7 days of radiotherapy and three of 10 if surgery was performed more than 7 days after finishing radiotherapy. (P = 0·36, Fisher's exact test).

Discussion

The Swedish Rectal Cancer Trial[1] has demonstrated impressive reductions in cancer mortality and morbidity rates with acceptable perioperative complication rates[2]. Much emphasis is placed on the radiotherapy technique which involves a short course at a relatively high dose to a minimized volume of tissue. Every attempt was made to adopt both the principles and practice of provision of preoperative radiotherapy.

Some surgeons report very low rates of local recurrence and good survival with optimal surgery[5,6]. It is argued that the increased adoption of optimal surgical techniques such as total mesorectal excision will result in lower local recurrence rates without the complications associated with radiotherapy. The combination of radiotherapy and total mesorectal excision may result in even lower rates.

The major difference in this selected series of patients undergoing preoperative radiotherapy is the fact that in the North Trent series all patients underwent a total mesorectal excision as described by Heald *et al.*[3].

The present results, in terms of procedures performed, postoperative deaths, perineal wound infection rates and wound infection rates, were similar to those reported in the initial report from the Swedish multicentre study[1]. The most obvious differences were the greater proportion of Dukes A tumours in the Swedish study, the high anastomotic leak rate in the North Trent series and the shorter hospital stay in the latter series.

Although the high incidence of Dukes A tumours in the Swedish study has been ascribed to downstaging by the radiotherapy[1], the large difference in histopathological classification in the North Trent series undoubtedly reflects patient selection. The ratio of abdominoperineal to anterior resection, although similar in the two studies, is higher than expected in the North Trent series. This almost certainly represents a selection bias with lower rectal cancers more likely than upper third tumours to get radiotherapy.

The high anastomotic leak rate in the North Trent series is worrying. While total mesorectal excision is associated with a higher anastomotic leak rate[7], a clinical leak rate of 15 per cent represents a significant increase in the rate reported in the Trent Audit[8], and the rates experienced by the surgeons involved in this study before the introduction of preoperative radiotherapy. These high anastomotic leak rates may represent a selection bias with more very low anastomoses in the North Trent series. Results of the Dutch trial of total mesorectal excision *versus* total mesorectal excision plus radiotherapy show a similar anastomotic leak rate of 15 per cent[9].

The long delay between surgery and radiotherapy, although improving dramatically in the latter part of this series, is unacceptable to patients and identifies the need for a major increase in resources if this technique is going to become established universally in the National Health Service. The need to avoid a delay between radiotherapy and surgery is highlighted by the dramatically increased rate of perineal wound breakdown if surgery was performed more than 7 days after completion of radiotherapy. The delays in surgery were a result of poor communication in the early part of the series ($n = 4$), cancelled theatre lists ($n = 2$) and cardiorespiratory disease requiring preoperative therapy ($n = 4$).

The high anastomotic leak rate in this series along with the high perineal wound infection rate and the reported poorer functional results[10] suggests that preoperative radiotherapy in combination with total mesorectal excision should be investigated further as part of the CRO7 trial or in carefully audited series.

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Original article

Behavioural treatment (biofeedback) for constipation following hysterectomy

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Background: Constipation after hysterectomy has been postulated to be due to pelvic nerve damage, but there may be emotional or reversible physical factors of pathophysiological relevance. The aim of this study was to determine whether such constipation is responsive to behavioural treatment.

Methods: Three groups of patients who had completed a course of biofeedback treatment were compared: women with no history of abdominal or pelvic surgery ($n = 25$), women for whom a hysterectomy had led to no change in bowel function ($n = 27$) and women who stated that their constipation was precipitated ($n = 18$) or severely worsened ($n = 8$) by hysterectomy. Pretreatment and post-treatment details about bowel function and symptoms were assessed using structured interview, and pretreatment whole-gut transit time and anorectal physiology testing were assessed for prognostic relevance.

Results: Follow-up after completing treatment was a median of 28 (range 12–44) months. Forty-eight of 78 patients considered that their constipation had improved with treatment; the proportion in each group was similar ($P = 0{\cdot}73$). Biofeedback reduced the need to strain, reduced abdominal pain, improved bowel frequency, and reduced laxative use to a similar degree in all three groups. Thirty-three of 53 patients with slow transit considered there was an improvement, compared with 15 of 22 with measured normal transit. Physiological testing did not predict outcome and did not differ between the three groups.

Conclusion: The majority of patients complaining of constipation induced or worsened by hysterectomy respond subjectively to behavioural treatment, in a similar proportion to those with idiopathic constipation. In contrast to the widely held view that nerve damage is responsible for symptoms, reversible factors are likely to be important in many patients.

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Introduction

Hysterectomy is the commonest gynaecological operation in the UK, performed in 28 per 10 000 women each year[1]. Urinary symptoms or dysfunction occur in up to 76 per cent of patients after total abdominal hysterectomy with bilateral salpingo-oophorectomy[2–4] and in 25 per cent of patients after hysterectomy with preservation of the ovaries[5,6]. New bowel symptoms occur in up to 43 per cent of women after hysterectomy[7–12], the most frequently reported being difficulty with evacuation. When treating these bowel symptoms after hysterectomy, dietary modification[13], laxatives[14–18], and surgical treatment of an enterocele or rectal prolapse[13,16,17] are often not effective.

Gut-directed biofeedback retraining has become an established therapy for idiopathic constipation[19–25], with more than half of all adult patients responding[17,26]. It helps patients with both slow and normal colonic transit, and those with or without paradoxical contraction[17,26,27].

In a large consecutive series of patients referred for management of intractable constipation, one-fifth reported that the onset of their symptoms was related to previous hysterectomy[26]. This study aimed to determine whether biofeedback is effective in such patients.

Posthysterectomy constipation has been attributed to autonomic denervation of the hind gut occurring as a complication of the procedure[12,14,15]. If this were the case, it might be expected that the condition would irreversible and not amenable to behavioural treatment. As part of the assessment, an objective measure of rectal innervation was used to establish the prevalence of possible hind gut denervation in patients complaining of constipation following hysterectomy, and to determine whether this marker of possible denervation could serve as a prognostic indicator.

Patients and methods

The only criterion for behavioural treatment is the subjective complaint of constipation which is unresponsive to dietary or drug treatment. All patients complain of either an excessive need to strain or an abnormally decreased bowel frequency[18]. All patients undergo a digital rectal examination in addition to radiological or endoscopic examination as appropriate. Patients with endocrine or other recognized causes of secondary constipation are excluded from this treatment.

Biofeedback therapy

Patients see a biofeedback therapist as an outpatient every 1–2 weeks, usually for four or five sessions. They lie on a couch on their right side facing the therapist and the electromyography display unit. A balloon is inserted into the rectum and inflated with 50 ml of air so that the patient has the sensation of a full rectum and thus the need to defaecate. Two adherent surface electrodes are placed adjacent to the anal opening to assess external anal sphincter function. The patient watches the trace of muscle activity and can see the pattern of electrical activity at rest and during voluntary contraction. The patient is then asked to observe the trace while attempting to expel the balloon. If there is an obvious increase, rather than the normal decrease, in activity, the patient is encouraged to strain without increasing sphincter activity so that its appearance continues to resemble the resting trace.

Patients are also taught how to strain effectively by using a propulsive force through bracing with their abdominal muscles. They are advised on normal defaecatory behaviour and bowel habits, including restricting the number of visits to the toilet for patients who make frequent defaecatory attempts during the day, or increasing the number of visits to the toilet for those with infrequent defaecation. The amount of time spent, and posture, in the toilet are also specified. The treatment includes gaining an appreciation about psychosocial factors of relevance. An attempt is made to get patients off oral laxatives, enemas and suppositories.

Patients

All the case records of women treated by biofeedback retraining for constipation over a 3-year period, and who had completed treatment at least 12 months previously, were reviewed. Seventy-eight consecutive contactable patients were identified from this group and were categorized into three groups as described below. Clinical details of the three groups of patients are shown in *Table 1*.

Table 1 Patient profiles for the three groups

	Group 1	Group 2	Group 3
No. of patients	26	27	25
Mean (range) age (years)	48 (37–75)	51 (34–71)	36 (24–63)
Mean age at onset of constipation (years)	30	27	17
Rectal prolapse	4	3	5
Rectocele*	8	7	7
Slow transit	19	18	16
Paradoxical contraction†	11	17	12
Psychological problems	0	3	3
Medical problems	3	2	1
Surgical problems	8	12	0

*Defined as an anterior rectal protrusion on proctography; †defined as pelvic floor contraction on straining on external sphincter electromyography

Group 1 (n = *26)*

Patients attributed the constipation to hysterectomy; they reported normal previous bowel function ($n = 18$) or considered that bowel function had been severely worsened by hysterectomy ($n = 8$).

Group 2 (n = *27)*

The onset of constipation in these patients, who had undergone hysterectomy, was not considered by the patient to be temporally related to the operation.

Group 3 (n = *25)*

This group comprised patients with constipation and no history of abdominal or pelvic surgery.

Review of medical notes

Notes were reviewed for details about medical history, bowel function and symptoms before treatment. Psychological factors which were routinely explored during biofeedback treatment were also recorded, including previous contact with a psychiatrist, psychologist or counsellor.

The results of physiological assessment and bowel transit before biofeedback were noted. Rectal electrosensitivity[28] was recorded as a possible prognostic marker, as abnormal sensory function reflects denervation. This previously validated technique assesses rectal sensation to an electrical stimulus using a bipolar electrode placed in the rectum 6 cm above the upper limit of the anal canal[28].

A transit time is performed in all patients before the commencement of biofeedback treatment. Three radiologically distinct sets of 20 radio-opaque markers are swallowed on successive days and a plain abdominal radiograph is taken 120 h after the ingestion of the first set of markers. The number of retained markers for each of the three sets is compared with a previously validated normal range[29]. Excessive retention of any one of the three sets is regarded as indicative of 'slow transit'.

Telephone interview

Each patient was interviewed by telephone by an investigator who had not been the patient's biofeedback therapist. Data were obtained using a questionnaire employed in a previous study[26]. Patients were asked about their age at onset of the constipation and its temporal relationship to the hysterectomy, bowel function before biofeedback, immediately after biofeedback and at the time of interview. Details included frequency of bowel action, details of laxative use, need to strain, need to digitate, and the presence of abdominal pain and bloating. Symptoms were assessed as either present or absent, to minimize the reporting of success in patients with only a partial response. Patients were also asked to give their opinion as to whether they considered biofeedback had helped them and specifically whether they believed the constipation had improved.

Statistical analysis

Student's t test was used to compare normally distributed data between the three groups. Fisher's exact test was used to analyse non-parametric clinical data. $P < 0{\cdot}05$ was considered statistically significant.

Results

Table 1 shows that the three patient groups were similar in terms of constipation history. Patients in groups 1 and 2 were significantly older than those in group 3 ($P = 0{\cdot}0006$ and $P < 0{\cdot}0001$ respectively). Patients in the first two groups also had a greater incidence of previous other medical and surgical problems. Forty-seven of 53 patients with previous hysterectomy (groups 1 and 2) had had an abdominal hysterectomy; six had had a vaginal hysterectomy.

The median length of follow-up after completing the course of biofeedback to the time of interview was 28 (range 12–44) months.

Table 2 Bowel symptoms

Group	Before biofeedback	Immediately after biofeedback	Long-term follow-up	P‡
Straining				
1	23	12	17	0·0007
2	21	15	15	0·07
3	23	17	17	0·05
P†	—	0·21	0·99	—
Pain				
1	11	5	8	0·06
2	16	8	8	0·03
3	14	7	5	0·04
P†	—	0·31	0·11	—
Low bowel frequency*				
1	6	4	6	0·36
2	15	9	10	0·09
3	11	6	9	0·12
P†	—	0·32	0·84	—
Normal bowel frequency*				
1	15	21	18	0·06
2	7	15	14	0·03
3	11	13	12	0·39
P†	—	0·14	0·58	—

*Low bowel frequency, less than three motions per week, normal bowel frequency, between three motions per week and three per day. †Values refer to the proportion of patients in the three groups with a symptom before and immediately after treatment, or before treatment and at long-term follow-up (χ^2 analysis), ‡values refer to whether a symptom was present in a significantly different proportion of patients on long-term follow-up *versus* before treatment, applied within each group of patients (Student's t test)

Overall 62 per cent (48 of 78) of patients considered that their constipation, specifically, had been improved by biofeedback. The proportion of responders in the three groups was similar: group 1, 71 per cent; group 2, 67 per cent; group 3, 56 per cent ($P = 0{\cdot}73$). Seventy-two per cent (56 of 78) considered that biofeedback had helped them feel generally better, the proportion in the three groups being similar: group 1, 77 per cent; group 2, 67 per cent; group 3, 73 per cent ($P = 0{\cdot}71$).

A comparison of bowel symptoms before and after biofeedback and on follow-up is shown in *Table 2*. Biofeedback reduced the need to strain and abdominal pain, and improved bowel frequency, in a similar proportion of each of the three groups. For each symptom there was no significant difference in incidence between the three patient groups before biofeedback and on long-term follow-up.

Laxative use was studied as an objective marker of benefit. Laxative use before and after biofeedback and on follow-up is shown in *Table 3*. There was a reduction in all forms of laxative consumption which was generally maintained at follow-up. There was a decrease in the use of laxatives in all three groups of patients, and no significant difference in laxative use between the three groups.

Twelve (15 per cent) of the 78 women studied had a rectal mucosal sensory threshold that was above the normal range. The proportion of patients with an abnormal threshold was similar in patients who had undergone hysterectomy (groups 1 and 2; eight (15 per cent) of 53 patients) and those who had not undergone hysterectomy (group 3; four of 25 patients).

Table 3 Laxative use

Group	Before biofeedback	After biofeedback	Follow-up
Oral laxative			
1	19	13	13
2	23	16	16
3	13	6	3
P*	—	0·65	0·36
Suppository			
1	3	2	1
2	8	2	1
3	8	3	4
P*	—	0·13	0·20
Enema			
1	5	1	4
2	5	4	4
3	5	4	4
P*	—	0·20	0·41

*Values refer to the proportion of patients in the three groups with a symptom before and after biofeedback, or before treatment and at follow-up (χ^2 analysis)

A transit study was performed in 75 of the 78 patients: 53 of these had slow transit, of whom 33 (62 per cent) subjectively improved. Twenty-two patients had normal transit, of whom 15 improved.

Discussion

This study has shown that behavioural treatment is effective in a majority of women complaining of constipation after hysterectomy. A retrospective study cannot ascertain definitively whether patients' surgery did in fact precipitate the bowel symptoms. Rather, it can be stated only that patients who present with bowel symptoms, and give this history, may respond to treatment.

There is a large overlap between gynaecological and bowel symptoms, and patients with bowel symptoms often attend a gynaecologist[8,30]. A proportion of these patients is likely to undergo hysterectomy because of pain, and this may contribute to worsening bowel symptoms in some patients. The psychological profiles of these two groups of patients are similar. Women who have undergone a hysterectomy have increased levels of anxiety and somatization, and an increased tendency to develop a variety of functional symptoms[31,32]. These psychological features are also common in women with constipation[13].

Several possible explanations may account for the pathogenesis of altered bowel and bladder function following hysterectomy. It was originally assumed that any symptomatic changes were due to emotional and sexual consequences of the operation[33–36]. The pre-existing psychological status of patients having a hysterectomy, together with the psychological effects of losing the womb, may be of relevance in some patients, and may account for the reversibility in some patients with behavioural treatment.

Alternatively, surgery has been postulated to damage the extrinsic autonomic nerve supply to the bladder and bowel[9,37]. The sacral efferent supply to the pelvic viscera is predominantly cholinergic and its loss would be expected to result in a loss of excitatory drive to the bowel. The present study found no evidence of hind gut denervation, as measured by quantitative sensory testing, in patients who had had a hysterectomy. The reversibility of symptoms after treatment would further suggest that, at least in some patients, there is unlikely to be permanent nerve damage.

A third possible explanation is that anatomical changes occur in the pelvis after surgery[38]. Removal of the uterus and its supporting structures may result in the potential to develop an enterocele, rectocele or rectal prolapse, all of which are known to be associated with difficult evacuation[39–41].

A similar proportion of patients with documented slow and normal transit improved with biofeedback treatment. It has previously been shown that subjective improvement, and improved bowel frequency, in patients with slow transit results in normalization of transit in most patients[27].

The patients who had had a hysterectomy were significantly older than those who had not had this operation. This is to be expected as hysterectomy most commonly occurs after childbearing is completed. The higher incidence of previous medical and surgical problems in the patients who had had hysterectomy may relate either to their older age, with more time to experience other illnesses, or to their predilection to seek surgical treatment, in general.

The proportion of patients responding to treatment was similar in those with and without a history of hysterectomy, and similar to the long-term results previously reported in a non-selected group[26]. The failure of some patients to respond may be due to irreversible neurological, psychological, physiological or structural factors.

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Original article

Abdominal content containment: practicalities and outcome

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Background: Alternatives to fascial closure of the abdominal wall are increasingly used in critically ill patients. They pose practical and logistical problems in management which are described in this single-institution study.

Methods: Between January 1994 and December 1997, 157 predominantly young male patients (100 trauma and 57 non-trauma) underwent temporary abdominal content containment (t-ACC) using plastic bags or polyglactin mesh. Indications for t-ACC were severe sepsis requiring reoperation, abdominal compartment syndrome, abdominal wall tissue loss or a combination of these. A total of 385 laparotomies were performed.

Results: Two t-ACC procedures failed owing to technical error and two were complicated by enteric fistulas. Six patients underwent early definitive abdominal closure within 15 days. The remaining survivors had a protracted hospital stay (mean(s.d.) 44·6(26·6) days) and all developed incisional hernias which were challenging to repair. The overall mortality rate was 44 per cent.

Conclusion: Plastic bags were cheaper and as effective as polyglactin mesh for t-ACC. Survivors require a multidisciplinary approach in management, undergo a protracted hospital stay and later need complex incisional hernia repairs.

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Introduction

Delayed fascial closure in abdominal surgery is often practised following 'damage control' strategies in major trauma[1,2], complicated emergency surgical procedures[3,4] and in severe intra-abdominal sepsis[5,6]. Technical problems or physiological decline associated with abdominal closure have generated numerous techniques to achieve abdominal content containment[4,7,8]. The variety of procedures that has been introduced or recommended implies that no specific technique is superior.

This study was a prospective analysis of experience with patients in whom abdominal content containment procedures were employed.

Patients and methods

Between January 1994 and December 1997, 157 patients underwent temporary abdominal content containment (t-ACC) procedures. Severe intra-abdominal sepsis necessitating multiple abdominal re-entries, incipient or established abdominal compartment syndrome as a result of gut oedema, acute tissue loss of the abdominal wall or a combination of these factors were the indications for this surgical approach.

Two methods of t-ACC were employed. Polyglactin mesh was used when further abdominal re-entries were unlikely. The mesh was stitched to the abdominal musculoaponeurotic sheath with a continuous polyglactin suture.

The second method utilized an empty, sterile, 1- or 3-litre plastic bag, of the type used for intravenous fluid administration or for urological irrigation, which was stitched with a continuous nylon suture to the edges of the rectus sheath or the skin dermis without any tension to the wound margins. This prevented musculoaponeurotic necrosis, and allowed 'free expansion' of the abdominal viscera to prevent a rise in intra-abdominal pressure. The seams of the plastic bag were left intact to prevent the sutures cutting through its margins and subsequent containment failure. At reoperation the plastic bag was always replaced with a new one. If no relaparotomies were needed, the plastic bag was removed between days 10 and 14 when the granulation tissue over the intestine was well enough established to prevent evisceration. *Fig. 1* demonstrates a t-ACC *in situ*. The initial dressing over the prosthetic material was a bulky absorbent gauze which required frequent changes, particularly if the porous polyglactin mesh was used. The dressing was retained in place using an adherent polyurethane wrapping (*Fig. 1*). With the plastic bag in place, the dressing remained as a bulky dry gauze over the wound. Following plastic bag removal the dressing was changed to paraffined gauze to prevent adhesion formation between the exposed intestine and the dressing itself. The paraffined dressing was changed to a hydrocolloid or hydrophilic polyurethane cover when the granulating surface was no longer septic and the induced secretions were minimal.

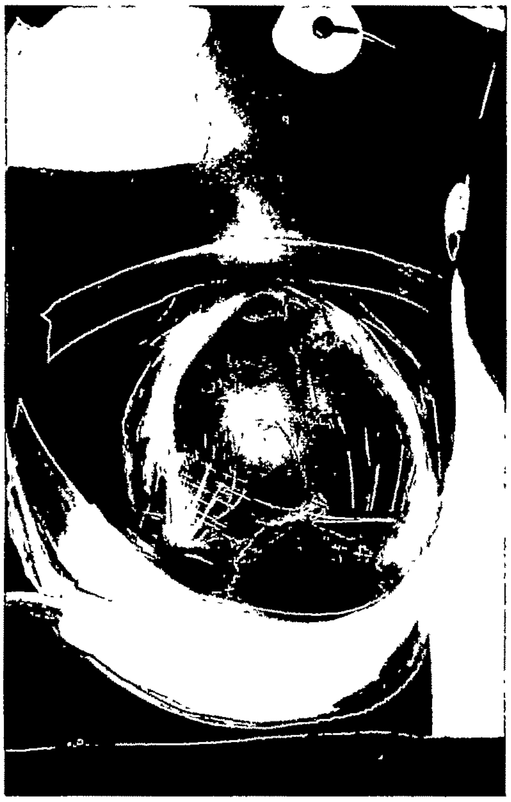

Fig. 1 Polyglactin mesh *in situ* with gauze in the lateral gutters and inferiorly, retained with adhesive polyurethane covering

Split skin grafting was the next phase of wound management and was undertaken when a healthy granulating bed free from streptococcal infection was ready. A 3 : 1 meshed split skin graft was used.

The abdominal wall hernia (*Fig. 2*) required closure when homoeostasis was re-established and the inflammatory process in the abdomen had resolved. Repair was usually performed in conjunction with maturity of the skin graft, which permitted easy removal from the underlying intestine and did not interfere with the major abdominal dissection necessary for abdominal wall reconstruction without a prosthesis.

Results

Table 1 details the deaths among patients with traumatic and non-traumatic pathologies. Of the former, the cohort with blunt polytrauma had the worst outcome: only six of 16 patients survived. Eighty-four penetrating injuries to the torso were divided into fire arm and stab wounds. Survival was significantly different between the fire arm (31 (48 per cent) of 65) and stab (17 of 19) wound groups ($P = 0{\cdot}0026$). Of the 57 patients with non-traumatic pathologies the group with acute necrotizing pancreatitis had the worst survival rate.

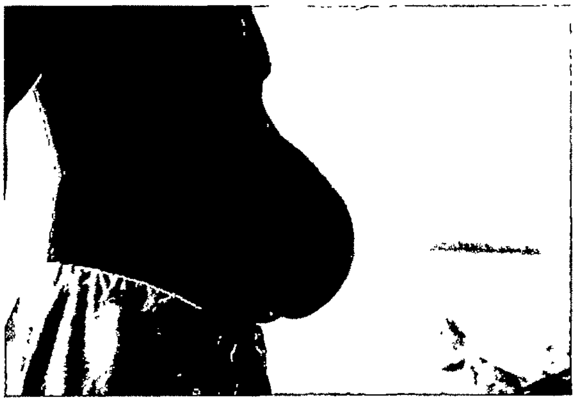

Fig. 2 Incisional hernia covered with a matured skin graft

Table 1 Deaths according to pathology

	No. of patients	Sex ratio (M F)	Deaths
Trauma	100	94.6	46 (46)
Blunt trauma	16	12 4	10 (62)
Penetrating trauma	84	82.2	36 (43)
Fire arm injuries	65	63·2	34 (52)
Stab injuries	19	19·0	2 (11)
Non-trauma	57	33:24	23 (40)
Peritonitis	39	22.17	12 (31)
Intestinal obstruction	11	8:3	6 (55)
Pancreatitis	6	3 3	5 (83)
Abdominal aortic surgery	1	0 1	0 (0)
Total	157	127.30	69 (44)

Values in parentheses are percentages

A total of 385 laparotomies were performed in the 157 patients with a mean of 2·5 (range 1–10) operations per patient. One hundred and one patients had one or two operations (total 161 laparotomies), of whom 51 patients (50 per cent) survived. Fifty-six patients had more than two operations (total 224 laparotomies), of whom 37 (66 per cent) survived. Patient survival for initial operations lasting less than 2 h was 68 per cent, while it dropped to 42 per cent when the initial operation was longer than 4 h.

Three hundred and twenty plastic bags and 40 polyglactin meshes were used. Eighty-eight patients had a t-ACC at the first operation, 75 with a plastic bag and 13 with a polyglactin mesh. The polyglactin mesh was always totally incorporated into the granulation tissue with no containment failure or intestinal fistulation, but with the constant occurrence of an incisional hernia.

Two containment failures occurred, one from this institution and the second in a patient transferred to this surgical department from a peripheral hospital. In both cases the operating surgeon cut seams off the margins of the plastic bag to correctly match the surgical wound gap, and the sutures cut through the plastic causing evisceration and requiring emergency replacement of the plastic bag.

The surgical principle of avoiding intraperitoneal anastomoses in a grossly contaminated field prompted the use of a diverting enterostomy in 18 patients at the first operation. Seven new enterostomies were created at second operations.

Two intestinal fistulas occurred in this series, one from this institution in the management of a septic abdomen and one referred from a peripheral hospital. In both patients the appearance of this complication was observed some time after removal of the plastic bag. The fistulas were managed conservatively initially, and surgically when a good nutritional status was restored by intravenous support. Both patients had abdominal wall closure at the time of repair of the intestinal fistula and were discharged a week after abdominal wall repair. Follow-up showed no parietal defects. In six patients definitive abdominal closure was possible between 10 and 15 days from the original open management of the intra-abdominal problems, because of early resolution of bowel oedema. Twenty-five patients had a split skin graft.

Definitive closure of the large abdominal wall defects was undertaken in 28 patients. Meticulous surgical dissection of the retracted edges of the sheath permitted closure without tension. In four patients long lateral releasing incisions were made in the external oblique muscle to effect closure. No meshes or muscular flaps were employed. The repair was never accomplished in under 2 h. Two patients have small ventral hernias that have not been repaired and four patients never returned for follow-up. The remaining patients had no clinically evident hernia at 6-week follow-up.

Discussion

Ogilvie[7], in 1940, was the first to purport the concept of prosthetic closure of the abdominal wall when the wound edges could not be approximated without tension. Abdominal wall substitutes were used initially when abdominal closure was problematic secondary to septic wound dehiscence[9]. Subsequently the modern concepts of 'laparostomy'[10], 'damage control'[1,11] and 'abdominal compartment syndrome'[12] were recognized and extended the indications for containment methods.

Initial metallic and synthetic materials used were rigid, brittle and susceptible to infection. Polypropylene mesh, with its low tissue reactivity and high tensile strength, was a much improved abdominal wall substitute even in grossly contaminated fields[13,14]. The successful use of polypropylene mesh has always been dampened by reports of intermediate- and long-term serious complications, particularly enteric fistulation[14–18]. Absorbable materials have also been used as temporary or permanent prostheses and rarely result in fistulation[19–21], although an incisional hernia has been the rule in survivors.

The gradual acceptance that no material fulfils the criteria of an 'ideal prosthesis', has led various authors to simpler solutions to this demanding problem[2,4]. One of these is represented by the 'Bogota Bag' eponym for plastic bag. The results of its use and particularly its efficacy in achieving containment have only been reported sporadically[2,22–24] or as acknowledgement of practice in developing countries[1,4,11]. Bendahan *et al.*[24] and Howard and Turner[23], in case reports, used a plastic bag as a temporary measure before definitive utilization of polypropylene mesh as a permanent substitute; this strategy was not employed in the present study and has been shown to be unnecessary. Fernandez *et al.*[2], in 1996, reported experience with the use of plastic bags in 15 trauma patients with critical injuries. Two prosthetic failures occurred but none of the other major complications often described with the use of polypropylene mesh. The vacuum pack reported by Brock *et al.*[22] is a more complex plastic bag-type containment described in 28 patients. Despite the drawback of its compulsory replacement in the operating theatre every 2–3 days, no major complications were observed. The economic advantage of this product was noted, an aspect further quantified by Fernandez *et al.*[2].

Hirshberg and Walden[25] suggested cutting the bag to shape but the present authors deliberately maintain the seams intact with a redundant prosthesis. This prevents containment failure, which only occurred in this study when the seams were cut. Furthermore, 'free expansion' of the oedematous intraperitoneal viscera is allowed, thus preventing an abdominal compartment syndrome and avoiding admission to the intensive care unit.

The high mortality rate in the cohorts of blunt abdominal trauma, acute necrotizing pancreatitis and those injured by firearms reflects the severity of the systemic inflammatory response in these individuals. In very few patients, in whom both general and wound factors are optimal, will early abdominal wall closure be possible, as in only six of the present patients. The inevitable parietal hernia is easily followed up on an outpatient basis. When the skin graft is regarded as 'mature' the patient is admitted for definitive closure of the abdominal wall defect. This is consistently time consuming as it requires meticulous tissue dissection in order to avoid the postoperative complication of closure under tension. The current limited data suggest this can usually be achieved without recurrent hernia.

There is no ideal prosthesis available for abdominal closure without tension in emergency circumstances; absorbable and non-absorbable prostheses have different drawbacks. Inexpensive materials should assume priority, if reliable containment with few complications and good long-term results in survivors can be achieved. This study shows that the plastic bag can achieve these goals and the authors consider it to be the method of choice.

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Original article

Validation of the gastrointestinal quality of life index for patients with potentially operable periampullary carcinoma

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Background: A disease-specific quality of life questionnaire is not available for patients with periampullary carcinoma, although cancer-specific questionnaires and the Gastrointestinal Quality of Life Index (GIQLI) have been used. The aim of this study was to validate the GIQLI for patients with periampullary tumours and to evaluate if subscales of the GIQLI could be identified to allow a more detailed assessment of the patients' quality of life.

Methods: Patients with periampullary carcinoma, included in a study concerning diagnostic laparoscopy, were asked about symptoms and completed a questionnaire comprising the Medical Outcomes Study (MOS) 24 questionnaire, the GIQLI and one question of the Rotterdam Symptom Check List (RSCL). Clinical interpretation and statistical factor analysis were used to identify subscales of the GIQLI.

Results: The GIQLI could be divided into four subscales, measuring physical well-being, mental well-being, digestion and defaecation. All four subscales had a good internal reliability and the construct validity was supported by the pattern of correlations with the MOS and RSCL as well as differences in subscale scores for patients with or without certain symptoms.

Conclusion: In patients with periampullary tumours the GIQLI can be divided into four subscales, measuring different aspects of quality of life. These subscales provide insight into the different problems affecting the patient.

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Introduction

Quality of life measurements have become increasingly important in surgical research and are nowadays often one of the endpoints of clinical trials, besides the more established outcome measures such as morbidity, mortality and survival rates[1–4].

Assessment of quality of life should be performed with questionnaires shown to be valid and reliable. The number of available generic- and disease-specific questionnaires necessitates careful questionnaire selection. For example, for patients with Parkinson's disease or Graves' ophthalmopathy disease-specific questionnaires have been developed[5,6]. By worldwide application of these questionnaires, comparable results and improved interpretation of quality of life studies can be achieved.

As part of a study performed in this hospital concerning patients with periampullary carcinoma, quality of life measurements were planned using both a generic and a disease-specific questionnaire. However, a disease-specific quality of life questionnaire was not available for patients with periampullary carcinoma. Cancer-specific questionnaires, such as the Rotterdam Symptom Check List (RSCL) or Functional Living Index – Cancer, are available, but were considered unsuitable for patients with periampullary carcinoma, because these patients suffer from many gastrointestinal complaints not included in these questionnaires[7–9]. The European Organisation of Research and Treatment for Cancer module specific for patients with pancreatic cancer is undergoing the final steps of validation and was not available at the start of this study. McLeod *et al.*[10] described quality of life of patients after a Whipple procedure by using the Gastrointestinal Quality of Life Index (GIQLI)[11], which is a self-administered, disease- or system-specific questionnaire. The GIQLI has been validated and tested with patients suffering from different gastrointestinal diseases but not in patients with periampullary carcinoma[12]. Until now, results of the GIQLI have always been presented as a single score, which is the sum of the scores of all 36 items. However the GIQLI comprises not only gastrointestinal symptoms but also other aspects of quality of life, such as social functioning and mental well-being. If subscales concerning different aspects of quality of life could be identified in the GIQLI, these subscales would allow assessment of the specific features of disease-related quality of life.

The aim of this study was to validate the GIQLI for patients with potentially resectable periampullary carcinoma and to determine if subscales for different aspects of quality of life could be identified.

Patients and methods

Between September 1995 and December 1997, all patients with a potentially resectable periampullary tumour (pancreatic head, distal common bile duct or papilla), who were included in a study concerning diagnostic laparoscopy and subsequent therapy, were asked to complete a quality of life questionnaire. Patients with jaundice were treated with insertion of an endoprosthesis 2–4 weeks before laparoscopy. Baseline measurements, including clinical assessment and completion of the questionnaire, were performed on the day of admission for diagnostic laparoscopy[13–15].

Questionnaire

The questionnaire comprised the generic Medical Outcomes Studies (MOS) short form, the disease-specific GIQLI and one question about overall quality of life from the RSCL[7,11,16]. Native bilingual German and Dutch speakers translated the GIQLI from German into Dutch and back, and thereafter the source and back translations were compared to produce a final Dutch version, which was tested in five patients with periampullary carcinoma.

The 24 questions of the MOS were summarized in seven subscales, ranging from 0 to 100; higher scores indicated better health. The 36 items of the GIQLI were scored from 0 to 4 and added up to a total score, ranging from 0 (worst) to 144 (best quality of life). The RSCL question was used as a single value with 1 representing worst and 7 representing best quality of life.

Analysis of Gastrointestinal Quality of Life Index

An analysis was performed to assess whether the 36 items of the GIQLI could be summarized into a few subscales, with each subscale measuring a different aspect of quality of life (for example mental or physical aspects). The first two investigators (E.J.M.N.v.D. and C.B.T.) divided the 36 items into subscales, based on clinical interpretation of the items. The results of this rational item keying were compared with the statistical division of the items into subscales[17].

The technique of factor analysis (also called principal component analysis) is based on the assumption that interrelations of certain items can be explained by underlying factors. For example the relation between questions about anxiety, stress and happiness can be explained by a factor named 'mental health', which represents the underlying factor. These factors determine the subscales in the questionnaire. Items within a subscale are thought to be highly correlated, whereas items between subscales are less correlated or not correlated at all.

In factor analysis all items are standardized with a mean of 0 and a variance of 1. The total variance in the questionnaire is therefore equal to the number of items, in this case 36. The total variance of the items within one factor is the 'eigenvalue' of that factor. The eigenvalue represents the amount of variance of the questionnaire (part of the 36) that is explained by the factor. An eigenvalue below 1 indicates no more variance than one single item. All factors with an eigenvalue of at least 1 were extracted in the factor analysis. The final subscale division was based on both the clinical interpretation and the statistical factor analysis.

Internal consistency, as a measure of reliability, was estimated by calculating Cronbach's alpha coefficient[18]. As recommended by Nunnally[19], internal consistency estimates of at least 0·70 were considered adequate. Correlations of the GIQLI subscales with the MOS-24 subscales and the RSCL were calculated to assess construct validity, which is the extent to which the questionnaire is able to measure what it claims to measure. Furthermore, the mean scores on the GIQLI subscales were compared between patients with and without symptoms, as scored by the physician at the first outpatient visit.

Results

One hundred and forty consecutive patients with periampullary tumours were asked to complete the questionnaire. Six of these patients refused to participate and two were not able to fill in a questionnaire owing to a language problem. Of the 132 questionnaires received, 125 questionnaires were complete. Patient characteristics and complaints at the time of completion of the first questionnaire are given in *Table 1*.

Four subscales were identified by the investigators: physical well-being (items 15–21), gastrointestinal symptoms (items 1–9 and 27–36), social well-being (items 22–26) and mental well-being (items 10–14).

Table 1 Characteristics of 125 patients who completed a questionnaire

	Patients	Reference population[20]
Age (years)*	63(10) (32–83)	
Sex (F:M)	51:74	
Karnofsky†	100 (80–100)	
Complaints (% of total)		
Jaundice	90	
Itching	66	
Nausea	38	
Vomiting	14	
Anorexia	62	
Weight loss	85	
Steatorrhoea	23	
Pain abdomen	45	
Pain back/side	18	
MOS subscales*		
Energy/fatigue	55(22)	—
Role functioning	37(45)	87
Mental health	65(22)	77
Social functioning	63(34)	92
Bodily pain	65(35)	74
Physical functioning	53(31)	86
Health perceptions	44(22)	72
RSCL*		
Overall quality of life	3·6(1·3)	

*Values are mean(s.d.) (range); †values are median (range). MOS, Medical Outcomes Study; RSCL, Rotterdam Symptom Check List

Table 2 Subscale division and factor loadings of the 36 items from the Gastrointestinal Quality of Life Index after factor analysis (with Varimax rotation)

Physical well-being subscale		
8	Enjoyed eating	0·58
15	Fatigue	0·70
16	Feeling unwell	0·73
18	Appearance	0·53
19	Physical strength	0·84
20	Endurance	0·82
21	Feeling unfit	0·80
22	Daily activities	0·61
23	Leisure activities	0·66
33	Nausea	0·51
Eigenvalue		5·9
Explained variance (%)		17
Gastrointestinal digestion subscale		
1	Pain in abdomen	0·53
2	Fullness in abdomen	0·57
3	Bloating	0·64
4	Flatus	0·48
5	Burping/belching	0·63
6	Abdominal noises	0·55
27	Regurgitation	0·56
28	Eating speed	0·54
32	Constipation	0·46
35	Heartburn	0·40
Eigenvalue		4·2
Explained variance (%)		12
Gastrointestinal defaecation subscale		
7	Bowel frequency	0·61
26	Impaired sexual life	0·54
30	Bowel urgency	0·68
31	Diarrhoea	0·43
34	Blood in stool	0·49
36	Uncontrolled stools	0·79
Eigenvalue		2·9
Explained variance (%)		11
Mental well-being subscale		
10	Coping with stress	0·73
11	Sad about illness	0·84
12	Nervous about illness	0·85
13	Happy with life	0·55
14	Frustrated by illness	0·83
Eigenvalue		2·7
Explained variance (%)		10
Items not included in a subscale		
9	Restricted eating	
17	Wake up at night	
24	Bothered by treatment	
25	Worsened relations	
29	Dysphagia	

Total explained variance was 50 per cent

Factor analysis was performed and ten factors with an eigenvalue of greater than 1 were extracted, accounting for 71 per cent of the variance of the 36 items. Several factor analyses were then performed, with the number of factors specified in advance. The solutions with five, four and three factors were examined especially, one factor more and one factor less than the expected four factors. The division into five factors, explaining 54 per cent of the variance, could be interpreted as a mental and a physical well-being subscale and three gastrointestinal subscales. The items within the three gastrointestinal subscales did not show interpretable differences in item content. The three-factor solution, explaining 42 per cent of the total variance, showed a physical well-being, a mental well-being and one gastrointestinal subscale, but some items considered gastrointestinal were also related to the physical well-being factor. The division into four factors was considered most satisfactory. The items with their factor loading are shown in *Table 2*. Factor loadings can be interpreted as the correlation between the item and the underlying factor; a high loading suggests that the item should be included in that factor.

Based on the statistical factor analyses and the clinical division by the investigators, four subscales were defined; the physical well-being subscale consisted of the items the investigators had defined (items 15–21) together with items 8 and 33, but without item 17. The mental well-being subscale was identical to the scale the investigators had defined (items 10–14). The first gastrointestinal subscale consisted of items concerning problems with digestion and the second of problems with defaecation. Four items had low (less than 0·40) factor loadings on every subscale and

Table 3 Descriptive statistics and reliability estimates for the Gastrointestinal Quality of Life Index ($n = 125$)

	Score*	Score range	Item mean score	No. of items	Cronbach's alpha
GIQLI					
Total	107(20)	0–144	2·96	16	0·93
Physical well-being	25(9)	0–40	2·48	10	0·91
Gastrointestinal digestion	32(6)	0–40	3·18	10	0·83
Gastrointestinal defaecation	21(3)	0–24	3·46	6	0·75
Mental well-being	14(4)	0–20	2·71	5	0·87

*Values are mean(s.d.). GIQLI, Gastrointestinal Quality of Life Index

Table 4 Pearson correlations of the Gastrointestinal Quality of Life Index subscales with the Medical Outcomes Study and the Rotterdam Symptom Check List

	Total GIQLI	Physical well-being	Gastrointestinal digestion	Gastrointestinal defaecation	Mental well-being
MOS					
Energy/fatigue	0·72	0·74	0·47	0·42	0·56
Role functioning	0·52	0·62	0·31	0·33	0·29
Mental health	0·53	0·39	0·33	0·32	0·78
Social functioning	0·70	0·77	0·42	0·50	0·44
Bodily pain	0·60	0·53	0·65	0·37	0·40
Physical functioning	0·54	0·63	0·36	0·40	0·27
Health perceptions	0·69	0·69	0·47	0·43	0·52
RSCL					
Overall quality of life	0·74	0·76	0·45	0·53	0·55

GIQLI, Gastrointestinal Quality of Life Index; MOS, Medical Outcomes Study; RSCL, Rotterdam Symptom Check List. All correlations are significant at 0·01 level (two tailed)

were not assigned to any of the subscales. Three items (1, 4 and 16) had factor loadings above 0·40 on more then one factor; these items were retained in the questionnaire and added to the subscale with the highest factor loading.

The total GIQLI and the four subscales had a normal distribution. *Table 3* shows the descriptive statistics and internal consistency reliability coefficients for the total GIQLI and the four subscales. Internal consistency reliability estimates were reasonable for the gastrointestinal defaecation subscale and high for the other subscales and total GIQLI. The mean item scores were low for the physical and mental well-being subscales (2·48 and 2·71 respectively) compared with those for the gastrointestinal digestion and defaecation subscales (3·18 and 3·46).

Correlations of the GIQLI subscales with the MOS-24 subscales and the overall quality of life item from the RSCL are shown in *Table 4*. Correlations were significant at the 0·01 level for all subscales with both the MOS and RSCL. Correlations of the GIQLI subscales were higher than the correlation of the total GIQLI and the MOS and RSCL.

The mean scores on the GIQLI physical well-being subscale were significantly lower for patients with anorexia, weight loss and abdominal pain than for those without, but were no different for any of the other symptoms. Patients with steatorrhoea, abdominal pain and back pain scored significantly lower on the gastrointestinal digestion subscale. Patients with jaundice and itching scored significantly higher on this digestion subscale compared with patients without these symptoms. Steatorrhoea and weight loss decreased the mean score on the GIQLI gastrointestinal defaecation subscale. Patients with abdominal pain had a significantly lower score on the GIQLI mental well-being subscale.

Discussion

This study was performed to validate the GIQLI as a disease-specific quality of life questionnaire for patients with potentially operable periampullary tumours. Using clinical interpretation and factor analysis, four subscales could be identified, assessing distinct dimensions of quality of life: physical well-being, mental well-being and two gastrointestinal aspects: digestion and defaecation.

Reliability estimates were high for all four subscales, indicating that the items within the subscales correlated well. To assess construct validity, correlations with other questionnaires were evaluated. Correlations between scales that assess the same kind of dimensions should be high to demonstrate validity. On the other hand, correlations between subscales that assess different dimensions should be low, to demonstrate the additional information obtained from each subscale. The GIQLI subscales were correlated with the generic MOS and RSCL scales, which are reliable and valid standardized measures of quality of life for patients with cancer and other patients[7,16,20,21]. The correlation pattern was as expected. High correlations between the GIQLI mental well-being subscale and the MOS mental health subscale as well as between the GIQLI physical well-being subscale and the MOS physical functioning subscale supported the construct validity of the GIQLI. As indicated by the subscale names, these correlations were expected and the GIQLI is therefore comparable to the MOS questionnaire for evaluation of patients' mental and physical well-being. The gastrointestinal subscales did not correlate as highly with the MOS subscales or the RSCL, except for the MOS pain subscale and the GIQLI gastrointestinal digestion subscale, which contains the item pain in the abdomen. These moderate correlations between the MOS and the GIQLI in a sample of patients with gastrointestinal symptoms show the additional value of these gastrointestinal subscales and support the belief that the gastrointestinal subscales indeed measure specific gastrointestinal problems affecting patients with periampullary carcinoma. Furthermore, the correlation pattern of the GIQLI subscales with the MOS and RSCL showed better discrimination of these subscales compared with the total GIQLI score, which supports the additional value of the subscales identified.

The differences between mean scores on GIQLI subscales for patients with and without symptoms indicate that the subscales of the GIQLI are able to discriminate between patients. However, the differences found were not completely as expected. The item nausea was assigned to the physical well-being subscale, but the mean score in this subscale was not lower for patients complaining of nausea. Patients with jaundice and itching scored higher on the digestion subscale than patients without these symptoms, probably because these symptoms occur in an early stage of the disease when digestive symptoms have not yet developed. These differences in expected and observed scores might be explained by the fact that patient–physician contact always includes interpretation of questions and answers. Furthermore, the GIQLI is specifically focused on the last 2 weeks, whereas the physician may not have explicitly questioned for symptoms during that time period, but as affecting the patient at the time of the interview or anytime before the interview. Nevertheless, the mean scores of the GIQLI subscales were significantly lowered in patients with certain symptoms.

This study dealt only with patients who had potentially operable periampullary cancer, before surgical treatment. Patients with periampullary cancer at another stage or those with other gastrointestinal diseases and complaints should be evaluated separately to further validate this subscale division of the GIQLI. These studies should increase confidence in its validity[1]. The GIQLI subscales should be calculated for patients with benign as well as malignant disease, in longitudinal studies, and should give reproducible results in stable patients. Additionally, interventional studies should be performed to assess whether the GIQLI is sensitive to clinically important changes.

Taking into account the validation aspects mentioned, this study demonstrated that the GIQLI could be divided into four subscales measuring different aspects of quality of life for patients with periampullary carcinoma. The development of subscales in the validated GIQLI obviated the laborious steps of validating a new questionnaire. The additional information obtained from the subscale division of the GIQLI gives insight into the different problems affecting a patient at the time of presentation. The GIQLI is appropriate as a disease-specific quality of life questionnaire for initial assessment of patients with potentially operable periampullary carcinoma.

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Original article

Specialized intestinal metaplasia in patients with gastro-oesophageal reflux disease

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Background: There is an increasing awareness that short (less than 3 cm) segments of Barrett's epithelium and macroscopically normal cardia epithelium may harbour specialized intestinal metaplasia (SIM), a premalignant phenotype. The prevalence of SIM was studied prospectively in an unselected population of patients attending for endoscopy, and the association of SIM with symptoms, lifestyle, medication, endoscopic oesophagitis and carditis was investigated.

Methods: Two hundred consecutive patients underwent endoscopy. Biopsies taken from just below the squamocolumnar junction were stained for SIM, and were analysed for carditis and *Helicobacter pylori* infection. A detailed questionnaire of symptoms, tobacco consumption and the use of proton pump inhibitors was completed.

Results: Forty-two patients (21 per cent) had SIM: 19 (15 per cent) of 126 in an endoscopically normal oesophagus, 15 (24 per cent) of 63 in a short segment of Barrett's epithelium and eight of 11 in classical Barrett's oesophagus. There was a significant association between SIM and carditis ($P < 0.0001$) and endoscopic oesophagitis ($P = 0.03$).

Conclusion: SIM is prevalent in patients undergoing endoscopy, does not correlate with symptoms or *H. pylori* infection, but is significantly associated with endoscopic and pathological markers of gastro-oesophageal reflux.

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Introduction

The traditional definition of Barrett's oesophagus, based on a macroscopic phenotype of columnar epithelium extending for 3 cm or more above the oesophagogastric junction, is now widely accepted as being arbitrary and of limited value[1]. The reasons for the current view are that only one of three histological types originally described[2], so-called specialized intestinal metaplasia (SIM), carries malignant potential[1] and that intestinal metaplasia has increasingly been recognized in shorter (less than 3 cm) segments of Barrett's oesophagus or biopsies of the gastric cardia in patients with macroscopically normal oesophageal and junctional mucosa[3–9]. The significance of SIM in these latter situations is unclear but may be of considerable importance in view of the alarming increase in incidence of adenocarcinoma of the oesophagus, oesophagogastric junction and cardia in the past two decades[10,11].

There are likely to be multiple factors governing the development of intestinal metaplasia but the clearest physiological association is with gastro-oesophageal reflux disease[12,13]. Intriguing recent evidence suggests that histological evidence of inflammation of the gastric cardia (carditis) is an early sign of reflux-induced inflammation that is tightly associated with the development of SIM[14,15].

The prevalence, aetiology, natural history and treatment implications of SIM in a short segment of Barrett's oesophagus and in a macroscopically normal oesophagus are thus of considerable current interest. This report highlights the lessons learned from a 4-month study on the prevalence of SIM, risk factors and its association with symptoms of reflux disease, *Helicobacter pylori* infection, and objective markers of reflux, in particular endoscopic oesophagitis and histological evidence of carditis.

Patients and methods

Subjects

Consecutive new patients attending for an elective endoscopic examination of the upper gastrointestinal tract, irrespective of indication, over a 4-month period were invited to participate in the study, which was approved by the Federated Hospitals Ethics Committee. Patients were excluded if they were unwilling or unable to give informed consent, or if they had any condition that precluded safe endoscopic biopsy (e.g. coagulopathy, oesophageal varices).

Symptoms

A structured questionnaire was designed (*Appendix 1*). This was completed by each patient before endoscopy and detailed gastro-oesophageal reflux symptoms, in particular heartburn, acid regurgitation, chest pain and dysphagia. A relevant medical history was included, detailing tobacco history, use of non-steroidal anti-inflammatory drugs, and recent (within 6 months) or current treatment with proton pump inhibitors.

Endoscopy

At the time of endoscopy the level of the squamocolumnar and gastro-oesophageal junctions was measured in centimetres from the incisor teeth or gums. The oesophagogastric junction was identified as the proximal margin of the gastric folds. The macroscopic appearance of the oesophagus was described as either Barrett's (3 cm or more of columnar epithelium extending above the gastro-oesophageal junction), short-segment Barrett's (less than 3 cm of columnar epithelium) or normal. Macroscopic oesophagitis, if present, was noted and graded according to the Hertzel[16] grading system as follows: grade 0, normal appearing mucosa; grade 1, mucosal oedema, hyperaemia and/or friability of mucosa; grade 2, superficial erosions involving less than 10 per cent of the mucosal surface of the distal 5 cm of oesophageal squamous mucosa; grade 3, superficial erosions or ulcerations involving 10–50 per cent of the distal oesophagus; and grade 4, deep peptic ulceration anywhere in the oesophagus or confluent erosions of more than 50 per cent of the distal oesophageal squamous mucosa.

In the absence of clinically evident Barrett's oesophagus, four biopsies were taken immediately distal to the Z-line (squamocolumnar junction) and a further biopsy from the gastric antrum. If Barrett's epithelium was identified, biopsies were taken from the Z-line in addition to four-quadrant biopsies at 2-cm intervals along the Barrett's epithelium. Biopsies of the squamous oesophageal mucosa were not taken routinely.

Histology

The specimens were fixed in 10 per cent buffered formalin and embedded in paraffin wax. Serial 4-μm sections were cut and stained with haematoxylin and eosin and Alcian blue at pH 2·5. A senior gastrointestinal pathologist who was unaware of the endoscopic and clinical data assessed the sections for the presence of SIM, *H. pylori* and carditis. SIM was strictly defined by goblet cells on haematoxylin and eosin staining, and intense blue staining of acid mucin in goblet cells by Alcian blue at pH 2·5[17]. Staining by Alcian blue in the absence of evidence of goblet cells was documented but was not classified as SIM. Dysplasia was recorded where present using criteria outlined elsewhere[18]. If biopsies of the junction revealed only squamous mucosa, this was considered as a sampling error and excluded from analysis. Carditis was characterized by the presence of eosinophil or plasma cell infiltration of the lamina propria and hyperplasia of the mucosa cells in the foveolar region[14,15]. *H. pylori* in antral biopsies was identified using criteria described previously[19].

Statistical analysis

Differences in clinical variables between groups (non-parametric data) were analysed by χ^2 analysis.

Results

Prevalence

Some 200 unselected consecutive patients fulfilling the inclusion criteria were studied. The indications for endoscopy were as follows: heartburn, regurgitation or dyspepsia (73 per cent), atypical chest pain (7 per cent), anaemia (4 per cent), weight loss (4 per cent), haematemesis (3 per cent) and miscellaneous (9 per cent). No patient was excluded.

There were 112 men and 88 women with a median age of 46 (range 15–93) years. Forty-two (21 per cent) had pathological evidence of SIM. Of 126 patients with an endoscopically normal oesophagus, 19 (15 per cent) had intestinal metaplasia, whereas 15 (24 per cent) of 63 patients with short-segment Barrett's oesophagus and eight of 11 patients with Barrett's oesophagus had SIM. Excluding the group of 11 patients with traditional Barrett's oesophagus, 34 (18 per cent) of 189 patients with a macroscopically normal oesophagus or a short segment of columnar epithelium had evidence of intestinal metaplasia.

Symptoms

The 42 patients with SIM were compared with the 158 patients with no evidence of SIM for symptoms including heartburn, regurgitation, dysphagia and odynophagia (*Table 1*). There was no significant difference between groups in these clinical parameters.

Table 1 Demographics, symptoms and risk factors

	SIM on biopsy ($n=42$)	No SIM ($n=158$)	P*
Mean (range) age (years)	49 (17–93)	45 (15–90)	0·9
Sex ratio (M : F)	25 : 17	87 : 71	0·6
Reflux symptoms			
Heartburn	19 (45)	88 (56)	0·2
Regurgitation	2 (5)	6 (4)	0·5
Dysphagia	3 (7)	9 (6)	0·5
Odynophagia	1 (2)	4 (2)	0·7
Risk factors			
Smoking history	15 (36)	66 (42)	0·5
Proton pump inhibitors	14 (33)	49 (31)	0·8
NSAIDs	5 (12)	11 (7)	0·2

Values in parentheses are percentages unless otherwise stated. SIM, specialized intestinal metaplasia; NSAIDs, non-steroidal anti-inflammatory drugs *χ^2 test

Table 2 Endoscopic and pathological findings

	SIM on biopsy ($n=42$)	No SIM ($n=158$)	P†
Endoscopic oesophagitis*	11 (26)	20 (13)	0·03
Antral gastritis	13 (31)	32 (20)	0·1
Helicobacter pylori	14 (33)	67 (42)	0·3
Hiatus hernia	7 (17)	21 (13)	0·6
Histological carditis	27 (64)	50 (32)	< 0·0001

Values in parentheses are percentages. *Grade 2–4 SIM, specialized intestinal metaplasia. †χ^2 test

Association with tobacco, non-steroidal anti-inflammatory drugs and proton pump inhibitors

Fifteen of 42 patients in the SIM-positive group were smokers compared with 66 (42 per cent) of 158 in the SIM-negative group (*P* not significant). There was no association between the presence of SIM and use of medication, in particular non-steroidal anti-inflammatory drugs and proton pump inhibitors (*Table 1*).

Endoscopic and histological analysis

The SIM-positive and -negative groups were compared for endoscopic oesophagitis, antral gastritis, *H. pylori* colonization and carditis (*Table 2*). Eleven of 42 patients with SIM had grade 2 or 3 (none grade 4) oesophagitis, compared with 20 (13 per cent) without SIM ($P = 0{\cdot}03$). Gastritis was evident in 13 of 42 patients with SIM and 14 were *H. pylori* positive, compared with 20 and 43 per cent respectively in the SIM-negative group (*P* not significant).

Carditis was significantly associated with the presence of SIM ($P < 0{\cdot}0001$). In the SIM-negative group, 106 of 158 patients had some staining with Alcian blue. Carditis was evident in 41 per cent of this group, a significantly greater ($P < 0{\cdot}001$) proportion than in the Alcian blue-negative group (seven of 48) but significantly less ($P < 0{\cdot}05$) than in the true SIM group. Carditis was not associated with the presence of *H. pylori* infection, as eight of 27 patients with SIM and carditis were *H. pylori* positive compared with 13 of 50 with carditis without SIM.

Discussion

There is compelling evidence linking SIM in short segments of Barrett's epithelium with adenocarcinoma of the lower oesophagus, oesophagogastric junction and gastric cardia[20,21]. Cameron *et al.*[22] noted intestinal metaplasia in ten of 24 cases of junction tumour compared with all cases of oesophageal adenocarcinoma. Metaplasia was present in 67 per cent of cases with tumours smaller than 6 cm but in only 17 per cent of larger tumours, suggesting that larger tumours may overgrow and obliterate the columnar epithelium from which they arise and that the overall association of SIM with adenocarcinoma for tumours in this area is underestimated.

This emerging recognition of a link between SIM and adenocarcinoma in resected specimens in patients who did not have Barrett's oesophagus by traditional criteria led Spechler *et al.*[3] in Boston to study SIM prospectively by taking two biopsies just below the squamocolumnar junction. In their seminal study of 142 unselected patients, 26 (18 per cent) had SIM on haematoxylin and eosin staining, 17 in short-segment Barrett's and in nine where the squamocolumnar junction and the gastro-oesophageal junction appeared as a straight line at the same level. Subsequent studies confirmed these findings and the addition of Alcian blue staining increased the sensitivity of capture of cases of metaplasia. For instance, Nandurker *et al.*[4] reported that SIM was detected in 46 (29 per cent) of 158 consecutive patients using a combination of haematoxylin and eosin and Alcian blue staining, whereas it would have been detected in only 23 (15 per cent) if haematoxylin and eosin alone were used. The experience of this unit and data from other reported series are shown in *Table 3*. The strict definition of SIM may possibly underestimate its true prevalence in the present series. None the less, if biospies were taken only where classical Barrett's oesophagus was evident, SIM, a premalignant phenotype, would have gone undetected in 34 of 42 patients.

There was no clear association between SIM and tobacco consumption or medication. Similarly, the prevalence of *H. pylori* infection did not differ between groups. This may not be surprising since epidemiological studies have failed to show an association between tumours of the oesophagus or

Table 3 Published and personal series on prevalence of specialized intestinal metaplasia

Reference	Year	*n*	Staining	Prevalence of SIM (%)	Prevalence of dysplasia (%)
Spechler *et al.*[3]	1994	142	H+E	18	1
Nandurker *et al*[4]	1997	158	H+E, Alcian blue	36	—
Trudgill *et al*[5]	1997	120	H+E, Alcian blue	18	—
Johnston *et al.*[6]	1996	170	H+E ± Alcian blue	9	0
Morales *et al*[7]	1997	104	H+E, Alcian blue	23	0
Clark *et al.*[8]	1997	241	H+E, Alcian blue	14	12
Sharma *et al.*[9]	1997	59	H+E, Alcian blue	—	8
Present study	1999	189*	H+E, Alcian blue	18	0

*Eleven patients with Barrett's epithelium longer than 3 cm were excluded. SIM, specialized intestinal metaplasia, H+E, haematoxylin and eosin

Table 4 Association of specialized intestinal metaplasia with symptoms, oesophagitis, carditis and *Helicobacter pylori* infection

Reference	Year	Reflux symptoms	Endoscopic oesophagitis	Histological oesophagitis	Carditis	*H pylori*
Spechler *et al.*[3]	1994	n.s	n s	Significant	—	—
Nandurker *et al*[4]	1997	n s.	n s	Significant	Significant	n s.
Trudgill *et al.*[5]	1997	n.s.	n.s	n.s.	—	—
Johnston *et al.*[6]	1996	Significant	n s.	n s.	—	—
Morales *et al*[7]	1997	n.s	n s.	—	—	Significant
Clark *et al*[8]	1997	All had reflux	—	—	—	n.s
Present study	1999	n s.	Significant	—	Significant	n.s

n.s , Not significant

cardia and *H. pylori*[23]. This finding is contrary, however, to that reported by Morales *et al.*[7], who identified SIM in 24 of 104 patients undergoing endoscopy with a strong association with *H. pylori* infection.

The association between reflux symptoms, endoscopic oesophagitis and histological evidence of oesophagitis is variable in published series (*Table 4*). There was no correlation between SIM and symptoms in this series despite a significant increase in evidence of endoscopic oesophagitis. Why this should be the case is unclear, although reduced visceral sensitivity to acid, an observation in traditional Barrett's oesophagus, is a possible mechanism[24]. The clearest pathological association identified was with inflammation of the cardia, supporting the suggestion that reflux-induced changes of inflammation and metaplasia of the epithelium of the cardia of the stomach is tightly associated with SIM and may be the first indicator of the effects of duodenogastric reflux. Oberg *et al.*[15] have reported a close association between carditis, SIM and reflux disease, and suggest a progression through a stage before the appearance of goblet cells where cardia mucosal cells may stain positive for Alcian blue. This hypothesis is controversial but is supported by the present finding that carditis was closely associated with SIM but was also associated to a lesser degree with Alcian blue-positive staining in the absence of clear evidence of goblet cells and SIM on haematoxylin and eosin staining.

The management implications, in particular the natural history of SIM and its optimum treatment once detected, await further study. In this study, no patient had evidence of dysplasia in SIM at presentation, but other studies[8,9] suggest a prevalence of approximately 9 per cent of low-grade dysplasia and an incidence on follow-up of up to 6 per cent per year, with some patients developing high-grade dysplasia. If SIM is caused by severe reflux disease, a fundamental question is whether it can be prevented or reversed. This is unclear, but a recent study[25] showed that antireflux surgery in 15 patients with SIM of the cardia resulted in complete loss of SIM in 11, whereas fundoplication in 45 patients with Barrett's oesophagus was followed by regression in only two patients. Thus, complementary studies not only on the natural history of short-segment SIM but also on the effects of antireflux surgery, and indeed maximal medical therapy, in patients with SIM and duodenogastric reflux are required.

In conclusion, SIM is prevalent in unselected patients undergoing upper gastrointestinal endoscopy, either in a short segment of macroscopic Barrett's epithelium or in the macroscopically normal cardia. Despite no clear association with symptoms, it is strongly associated with histological evidence of carditis and endoscopic oesophagitis. Since SIM is the only phenotype for tumorigenesis for an upper gastrointestinal cancer that has increased markedly in incidence in the past 20 years, biopsies of the columnar epithelium should be obtained to identify these patients for follow-up and facilitate further studies.

Appendix 1

Symptom Questionnaire

Name Date of examination
Address Endoscopist

MRN Consultant
TEL
DOB

Indication for endoscopy

GORD Symptoms Duration (mths)

Heartburn	mild	moderate	severe
Regurgitation	mild	moderate	severe
Dysphagia	mild	moderate	severe
Odynophagia	mild	moderate	severe
Chest pain	mild	moderate	severe

Mild = symptoms not present every day
Moderate = symptoms present every day
Severe = symptoms affecting daily life

Alcohol (units/week)
Smoking (cigs/day)

**Questionnaire to be complete by each patient in the presence of a doctor

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Correspondence

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Prospective study of symptoms and gastro-oesophageal reflux 10 years after posterior partial fundoplication

Sir

We read with interest the article by Franzén *et al.* (*Br J Surg* 1999; **86**: 956–60) describing the long-term outcome of patients following posterior 270° fundoplication for gastro-oesophageal reflux disease. The paper concludes that partial fundoplication is an effective procedure in most patients. Those with severe (Savary grade III or IV) oesophagitis, however, had an increased chance of clinical and pathophysiological recurrence and the authors concluded that partial fundoplication was not successful in controlling reflux disease in this group of patients. Are the authors suggesting that, in these patients, a 360° fundoplication should be used and that surgery should be tailored depending on the results of preoperative endoscopy?

We have analysed the results of physiological investigations performed on 130 consecutive patients before and after laparoscopic 360° fundoplication and found a highly significant correlation between preoperative and postoperative distal oesophageal acid exposure time (AET; percentage of total time pH < 4; $r^2 = 0{\cdot}13$, $P < 0{\cdot}0001$, unpublished data). Therefore, patients with higher AET on preoperative pHmetry are more likely to have continued pathological reflux following surgery. Our results concur with those of Franzén *et al.* despite different methods in stratifying disease severity. This suggests that patients with high AET, who represent the group most in need of surgery, are more likely to have residual reflux regardless of the type of fundoplication. There remains insufficient evidence, however, to suggest that the results of preoperative investigations should be used to tailor surgery.

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Authors' reply

Sir

Thank you for the opportunity to reply to this letter. All patients with different stages of oesophagitis before operation, had normal distal oesophageal AET 6 months after operation. We, therefore, conclude that the partial fundoplication was successful when assessed at early follow-up. Some 10 years later, however, we found more recurrences in the group that had severe oesophagitis before operation. Perhaps similar results would have been obtained after Nissen fundoplication? The patients with end-stage disease and oesophageal shortening are difficult to treat with any type of antireflux operation.

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Multimodal therapy for squamous carcinoma of the oesophagus

Sir

In his review of therapy for oesophageal carcinoma Dr Lehnert (*Br J Surg* 1999; **86**: 727–39) concluded that neoadjuvant treatment confers a survival advantage only if surgical therapy is suboptimal and that 'poor results of surgical treatment were improved by neoadjuvant therapy… whereas better surgical results were not'. This conclusion is unwarranted because one of the studies refers exclusively to squamous carcinoma where only 23 per cent of patients had positive[1] lymph nodes, while the other refers to adenocarcinoma where 82 per cent had positive lymph nodes or stage 4 disease[2]. We feel strongly that patients with node-positive disease should be recruited as most have advanced disease at presentation.

Furthermore, disease stage determines sample size. Using Freedman's method to estimate sample size we calculated that 190 patients were needed to detect a 20 per cent improvement on a 2-year survival rate, with a power of 80 per cent and an α of 5 per cent[2]. If most patients had early disease, sample size would have increased accordingly.

The role of neoadjuvant therapy in the treatment of squamous carcinoma remains unclear because studies have been poorly designed and included inadequate numbers. One recent trial could not 'find' a significant survival difference between a 15 and 32 per cent survival rate at 3 years[3]! Of the seven randomized trials reviewed by Dr Lehnert, only four used surgery controls and, of those, only two used 5-fluorouracil, and one of these used an inadequate radiotherapy protocol. We conclude that the role of neoadjuvant therapy in the treatment of squamous carcinoma is unproven due to lack of evidence.

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1 Bosset J-F, Gignoux M, Triboulet J-P, Tiret E, Mantion G, Elias D *et al.* Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med* 1997; **337:** 161–7.

2 Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TPJ. A prospective randomised trial of multimodal treatment plus surgery *versus* surgery alone for oesophageal adenocarcinoma *N Engl J Med* 1996; **335:** 462–7.

3 Urba S, Orringer M, Turris A, Whyte M *et al* A randomized trial comparing surgery (S) to preoperative concomitant chemoradiation plus surgery in patients (pts) with resectable esophageal cancer (CA): updated analysis. *Proc ASCO* 1997; **16:** A227.

Authors' reply

Sir

The kind interest expressed by Messrs McDonnell and Walsh as representatives of the Royal College of Surgeons in Ireland in the multimodal treatment of squamous cancer of the oesophagus is sincerely appreciated. However, my review did not conclude that 'neoadjuvant treatment confers a survival advantage only if surgical therapy is suboptimal' or that 'poor results of surgery were improved by adjuvant therapy, whereas better results were not' (as Messrs McDonnell and Walsh suggest). The relevant paragraph clearly states 'no definite conclusions should be drawn regarding the efficacy of neoadjuvant radiochemotherapy. It is possible that adjuvant or neoadjuvant treatment is effective only in patients undergoing optimal surgical treatment. Conversely, it might be speculated that neoadjuvant treatment can confer a survival advantage only if surgical therapy is suboptimal. Indeed, it would appear from randomized studies, that poor results of surgical treatment were improved by neoadjuvant therapy of oesophageal adenocarcinoma[1,2], whereas better surgical results were not improved by neoadjuvant treatment[3]. Such speculation will remain unresolved...'.

The correspondents might also re-examine the report by Bosset *et al.*[3]. They argue that only 23 per cent of patients had positive lymph nodes, but what they quote is the result of clinical staging. The pathological staging (which appears on the following page of the article) details a much higher metastatic rate of 55 per cent (70 per cent when palliative patients are included). A statistical issue is then taken up, but the reason for this is not entirely clear. Suffice it to say that disease stage is *not* entered into the equation when sample size is calculated. Consultation with a statistical advisor should easily clarify the variables needed to determine sample size. Messrs McDonnell and Walsh also express a strong feeling that node-positive patients should be recruited, but they fail to specify which treatment precisely they wish to recommend. This would be of particular interest because their own study of neoadjuvant radiochemotherapy with 5-fluorouracil/40 Gy did not show a significant survival benefit for squamous cancer of the oesophagus[4]. Whatever treatment they have in mind for node-positive patients, they must accept that the preoperative diagnosis of lymph node metastases is highly inaccurate, even with the most up-to-date imaging techniques.

In summary, it is a little difficult to get the gist of this communication. Nevertheless, I am glad to share the view that the value of neoadjuvant radiochemotherapy for the treatment of squamous carcinoma is yet unproven. A joint effort with clear concepts, carefully designed trials and accurate interpretation of the results will eventually allow the answer.

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1 Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TPJ. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996; **335:** 462–7.

2 Urba S, Orringer M, Turrisi A, Whyte R, Iannettoni M, Forastiere A. A randomized trial comparing surgery to preoperative concomitant chemoradiation plus surgery in patients with resectable esophageal cancer: updated analysis. *Proc ASCO* 1997; **16:** A983.

3 Bosset JF, Gignoux M, Triboulet JP, Tiret E, Mantinon G, Elias D *et al.* Chemoradiotherapy followed by surgery compared with surgery alone in squamous cell cancer of the esophagus. *N Engl J Med* 1997; **337:** 161–7.

4 Walsh TN, Noonan N, Hollywood D *et al.* Multimodality treatment plus surgery *versus* surgery alone for oesophageal squamous carcinoma. In: Peracchia A, ed. *Recent Advances in Diseases Of the Oesophagus.* Monduzzi Editori: Bologna, 1996: 451.

Prevalence of aortic aneurysm in men with a history of inguinal hernia repair

Sir

We read with interest the paper by Pleumeekers *et al.* (*Br J Surg* 1999; **86**: 1155–8) reporting an association between inguinal hernia and abdominal aortic aneurysm (AAA). As the authors suggest, these findings are in keeping with those of Lehnert and Wadouh[1]. Similarly, Cannon *et al.*[2] reported a higher prevalence of inguinal hernia in patients with AAA than in those with Leriche's syndrome

We have reservations about the authors' conclusion that, as part of a selective screening programme, ultrasonography of the abdominal aorta might be considered before operation for inguinal hernia. In a review of 149 patients presenting to our hospital with AAA, 17 per cent had a history of inguinal hernia. The median duration between presentation of the hernia and the AAA was 13 (interquartile range 2·5–23) years. Similarly, Cannon *et al.*[2] reported that 'herniation appeared 12–13 years before the AAA became manifest'. In the series by Lehnert and Wadouh[1], 45 per cent of the patients had undergone hernia repair more than 10 years before presentation with the aneurysm. The rate of increase in diameter of an AAA is approximately 10 per cent per annum[3]. These figures suggest that many of the patients who potentially will develop such a lesion will have no evidence of this at the time of presentation with their hernia. A single ultrasonographical examination at the time of hernia repair would, therefore, not provide adequate screening. If inguinal hernia is to be considered an index for AAA screening, these patients will require sequential ultrasonography over a substantial period of time.

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1 Lehnert B, Wadouh F High coincidence of inguinal hernias and abdominal aortic aneurysms. *Ann Vasc Surg* 1992, **6:** 134–7.
2 Cannon DJ, Casteel L, Read RC. Abdominal aortic aneurysm, Leriche's syndrome, inguinal herniation and smoking. *Arch Surg* 1984, **119:** 387–9.
3 Cronenwett JL, Sargent SK, Wall MH, Hawkes ML, Freeman DH, Dain BJ *et al* Variables that affect the expansion rate and outcome of small abdominal aortic aneurysms. *J Vasc Surg* 1990, **11:** 260–8.

Value of splenic preservation during distal pancreatectomy for chronic pancreatitis

Sir

Govil and Imrie (*Br J Surg* 1999; **86:** 895–8) conclude that spleen-preserving distal pancreatectomy (SPP) may delay diabetes. This is not our experience in the treatment of patients with chronic pancreatitis[1]. The spleen plays no role in glucose metabolism or insulin secretion and SPP is unlikely to delay diabetes. The authors provide no data from glucose tolerance tests to support their conclusions.

Diabetes in patients with chronic pancreatitis depends on a number of factors; patients with severe disease in the distal pancreas may lose exocrine and endocrine function because islets are concentrated in the distal pancreas[2]. For those requiring resection, diabetes is dependent on the functional islet mass left *in situ* or delivered as an autologous islet transplant[3,4]. Rarely, autoimmune chronic pancreatitis leads to diabetes but splenectomy, as opposed to SPP, might theoretically delay diabetes[5].

Govil and Imrie may have misinterpreted their results. Splenectomy is often necessary only when the pancreas is severely diseased and the splenic vessels cannot be separated. It is likely that the severity of disease was greater in those requiring splenectomy. These patients probably had a marginal islet mass before surgery and had more of the pancreas resected. Moreover, some patients having SPP had a rim of pancreatic parenchyma left encasing the splenic vessels. Taken together, the delay in diabetes in patients having SPP was because they had a greater functional islet mass left *in situ.*

It would be useful to know what happened to the patients who had a poor result after surgery, especially if they had a rim of diseased pancreas left encasing the splenic vessels.

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1 White SA, Sutton CD, Robertson GSM, Berry DP, Rees Y, Dennison AR. Spleen preserving total pancreatectomy for chronic pancreatitis. *Br J Surg* 1999; **86** (Suppl 1): 73.
2 Wittingen J, Frey CF. Islet concentration in the head, body, tail and uncinate process of the pancreas. *Ann Surg* 1974; **179:** 412–14.
3 Wahoff DC, Papalois BE, Najarian JS, Kendall DM, Farney AC, Leone JP *et al.* Autologous islet transplantation to prevent diabetes after pancreas resection. *Ann Surg* 1995, **222:** 562–79.
4 White SA, Burden AC, Pollard C, David JE, Swift SM, Clayton HA *et al.* Normal HBA1C after pancreatic islet autotransplantation. *Br J Surg* 1998, **85** (Suppl. 1): 47.
5 Tetsuhide ITO, Nakano I, Shujiro K *et al.* Autoimmune pancreatitis as a new clinical entity. *Dig Dis Sci* 1997; **42:** 1458–68.

Book reviews

Introduction to Surgery. 3rd ed.

D. H. Levien.

227 × 151 mm Pp. 303 Illustrated 1999. Philadelphia, Pennsylvania: W. B Saunders. £22.

This book, now in its third edition, aims to provide an introduction to surgery through a series of case- and problem-oriented case presentations. It is easily read over the space of a few days and provides an excellent foundation for medical students starting surgical attachments and first year surgical house officers. The presentations are particularly interesting and informative for students, who are likely to encounter similar cases in a surgical attachment. The relevant history in each instance is presented and subsequent investigations and treatment are outlined, accompanied by excellent line diagrams to illustrate surgical anatomy and technique. Using this background, the cases are discussed to highlight the principal features of each clinical scenario. The topics covered include wound management, tubes and drains, critical care and trauma, as well as the usual chapters on the gastrointestinal tract. This provides students with a comprehensive, patient-oriented rather than system-oriented introduction to surgery which many will find useful. However, the text assumes a certain level of knowledge of jargon and terminology with which the target audience may not be familiar and may require reference to other texts to gain full value from the book. The volume is principally aimed at an American audience and includes a useful chapter on 'Milestones in Surgical Training' for those interested in pursuing a career in surgery in the American system. The final chapter on 'Educational Resources in Surgery' lists an excellent bibliography, but again most references are to American texts. In conclusion this book provides a useful introduction for medical students and residents beginning a surgical attachment. It is easily read and is informative but is aimed at an American audience.

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Critical Limb Ischaemia

A. Branchereau and M. Jacobs (eds).

278 × 217 mm. Pp. 267. Illustrated. 1999. Armonk, New York Futura $120.

This book on critical limb ischaemia follows the successful format established at other vascular meetings, where invited speakers are asked to submit a chapter for a book which is available for the participants at the meeting. The advantages of such a format are that they tend to be written by recognized authorities in their field and that they are up to date. The disadvantages include the inevitable overlap between chapters and contradictory statements between differing authors. The former might be avoided by more interventional editing and the latter helped by editorial comments at the end of each chapter discussing any inconsistencies. It is a pity that, although the meeting is from the European Vascular Course, the spelling is American. Each chapter starts in italics and continues in narrow print (with up to 19 words per line), both of which are difficult to read. Perhaps two columns would have been easier on the eye, and more attention might have been paid to the grammatical content. These gripes aside, it provides a very good overview of the subject, ranging from the pathophysiological basis of the disease to treatment, including surgical, radiological and medical therapy. All clinicians practising in this field will find it extremely useful; trainees in all disciplines would benefit from reading this before their final examinations.

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Clinical Surgery in General. RCS Course Manual

R. M. Kirk, A. O. Mansfield and J. P. S. Cochrane (eds).

246 × 189 mm. 453pp. 1999. Illustrated. London Churchill Livingstone £47·95.

This book succeeds in emphasizing to surgeons the art, science and ethos of the non-operative aspects of surgery. It is the Royal College of Surgeons of England course manual to be used in conjunction with the STEP distance learning course. It is also a stand-alone textbook and, as such, it has some deficiencies, but there are excellent relevant references at the end of each of its 49 chapters. By keeping to a reasonable size, some of the chapters are quite intense ('Immunity in Surgery' in six pages), but in their quest for brevity the editors are to be congratulated on keeping the text readable and not degenerating to lists. In the chapter on 'Clinical History and Examination' there are some contradictions of style, quotable quotes such as 'investigations - the instruments for vacillation' and the less quotable 'look, feel, percuss, listen', surely 'inspection, palpation, percussion, auscultation' has less of a 'Janet and John' feel to it! The eight sections cover emergencies, patient assessment, preoperative and postoperative aspects, operative issues, malignant disease, complications and general considerations. These last chapters are particularly useful as they are not easily found in other publications. Clinical governance and risk management are mentioned; I expect they will warrant separate chapters when the fourth edition is produced. This is a book for those taking the basic and intercollegiate examinations of the royal colleges of surgeons, not least because it is likely to be an important 'aide memoire' for those conducting the examination.

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Scientific Surgery

Palli D, Russo A, Saieva C, Ciatto S, Roselli Del Turco M, Distante V *et al.* Intensive *versus* clinical follow up after treatment of primary breast cancer: ten year update of a randomized trial. *JAMA* 1999; **281**: 1586

The original study included 1243 patients The 10-year survival rate was similar after clinical (31·5 per cent) and intensive (34 8 per cent) follow-up

Cooper JS, Gou MD, Herskovic A, MacDonald JS, Martenson Jr JA, Al-Sarraf M *et al.* Chemoradiotherapy of locally advanced esophageal cancer: long term follow-up of prospective randomized trial. *JAMA* 1999; **281**: 1623–7.

In the 196 patients included, the 5-year survival rate was significantly better after chemoradiotherapy (26 per cent) than after radiotherapy alone (none)

Banani SA, Talei A. Can oral metronidazole substitute parenteral drug therapy in acute appendicitis. A new policy in the management of simple or complicated appendicitis with localized peritonitis: a randomized controlled clinical trial. *Am Surg* 1999; **65**: 411–16.

Some 1083 operations were studied. The wound infection rates were similar when stratified for severity of appendicitis, as was the rate of pelvic abscess

Porter JM, Ivatury RR, Azimuddin K, Swami R. Antioxidant therapy in the prevention of organ dysfunction syndrome and infectious complications after trauma: early results of a prospective randomized trial. *Am Surg* 1999; **65**: 478–85.

This small study including 18 patients found that use of antioxidants (N-acetylcysteine, selenium and vitamins C and E) reduced organ dysfunction and infective complications, but there were no deaths in either group

Ferzli GS, Frezza EE, Pecoraro Jr AM, Ahern KD. Prospective randomized study of stapled *versus* unstapled mesh in a laparoscopic preperitoneal inguinal hernia repair. *J Am Coll Surg* 1999; **188**: 461–5.

The trial included 100 hernia repairs; there were no complications or recurrent hernias (mean follow-up 8 months), but avoiding the use of staples was cheaper

Hilgert RE, Dorner A, Wittkugel O. Comparison of polydioxanone (PDS) and polypropylene (Prolene) for Shouldice repair of primary inguinal hernias: a prospective randomised trial. *Eur J Surg* 1999; **165**: 333–8.

Some 233 hernias in men were studied There was no significant difference in recurrence rates (total 5 per cent) after a minimum of 2 years six after PDS and five after Prolene

Corazzone A, Bonavina L, Segalin A, Ceriani C, Peracchia A. Endoscopic palliation of oesophageal cancer: results of a prospective comparison of Nd:YAG laser and ethanol injection. *Eur J Surg* 1999; **165**: 351–6

Forty-seven patients were studied There were no significant differences in symptom control or survival (median 6 months in both groups)

Brisinda D, Maria G, Bentivoglio AR, Cassetta E, Gui D, Albanese A. A comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure. *N Engl J Med* 1999; **341**: 65–9.

The rate of healing was higher after 2 months in patients who had botulinum toxin (96 *versus* 60 per cent, $P = 0{\cdot}005$) in this study of 50 patients

Ubbink D Th, Spincemaille GHJJ, Prins MH, Reneman RS, Jacobs MJHM for the Dutch Spinal Cord Stimulation Study Group. Microcirculatory investigations to determine the effect of spinal cord stimulation for critical leg ischaemia: the Dutch multicenter randomized controlled trial. *J Vasc Surg* 1999; **30**: 236–44.

Some 120 patients were randomized to spinal cord stimulation (SCS) or best medical treatment All patients had microcirculatory assessment with laser Doppler, capillary microscopy and transcutaneous oxygen measurement. Although clinical outcomes were similar, microcirculatory tests identified a subgroup who benefited from SCS.

Sbarigia E, Darioviizza C, Antonini M, Speziale F, Maritti M, Fiorani B *et al.* Locoregional *versus* general anesthesia in carotid surgery: is there an impact on perioperative myocardial ischemia ? Results of a monocentric randomized trial *J Vasc Surg* 1999; **30**: 131–8.

A total of 107 patients were randomized. Patients who had locoregional anaesthesia had fewer episodes of myocardial ischaemia, most of which were postoperative

Stafford RE, McGonigal MD, Weigelt JA, Johnson TJ. Oral contrast solution and computed tomography for blunt abdominal trauma. *Arch Surg* 1999; **134**: 622–7.

Some 394 patients who needed abdominal computed tomography were included. The addition of contrast, which was inserted using a nasogastric tube, delayed the investigation but did not improve its accuracy

Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med* 1999; **341**: 137–41.

Eleven of 21 included patients were randomized to receive intravenous neostigmine Although several developed abdominal pain and vomiting, ten of 11 had prompt colonic decompression, compared to none in the control group

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The Editorial Board of The *British Journal of Surgery* encourages submission of review articles on topics of interest. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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This must not exceed 200 words and should be presented in a structured format. **Background**· state why the study was done and its main aim. **Method.** describe patients, laboratory material and other methods used Clearly identify the nature of the study, i.e. randomized controlled trial, retrospective review, experimental study, etc. **Results**: state the main findings including important numerical values. **Conclusion**: state the main conclusions but controversial or unexpected observations may be highlighted.

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Use abbreviations *sparingly*. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension. Abbreviations must be used consistently and must be defined on first use.

Numbers and units

Use the decimal point, not a comma, for example 5·7. Use a space and not a comma after thousands and multiples thereof, for example 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg)

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For detailed guidance on the handling of statistical material consult *Br J Surg* 1991; **78**: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, the chosen end-points and justify the sample size Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; **276**: 637–9).

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Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

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Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value. Actual *P* values should be reported to two decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

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Take great care in your interpretations. Do not place undue emphasis on secondary analyses

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Type the references with double spacing in the Vancouver style (see **Preparation of manuscripts**). Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted.

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Leading article

Neuroendocrine tumours of the pancreas

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Neuroendocrine pancreatic tumours (NPTs) may be either functioning (and associated with a specific clinical syndrome due to hormone overproduction) or non-functioning. Their incidence is about 0·4 per 100 000 population; non-functioning tumours form the biggest group (30–40 per cent), followed by gastrinomas. All NPTs other than insulinomas are malignant in over 50 per cent of cases and so treatment must be directed at both tumour growth and hormone excess. The commonest cause of death nowadays is liver failure from tumour progression[1]; this has become evident since the development of medical treatment (proton pump inhibitors, somatostatin analogues) that can control hormonal symptoms. Today treatment against the tumour itself is important for long-term survival. Several new therapeutic options have been introduced over the past 20 years and a multimodal approach is warranted in which different therapies may be given synchronously and metachronously. Treatment must be individualized according to the type of tumour and the overall status of the patient.

Improved diagnosis has come through biochemistry. Measurement of plasma levels of chromogranin A not only allows early detection of residual or recurrent small NPTs, but also provides a reliable tumour marker to monitor the effect of treatment in all patients, irrespective of syndrome or functionality[2]. Increasing knowledge in tumour biology should provide new tools to guide treatment options. Already, the expression of the proliferation marker Ki-67 has been shown to correlate with prognosis and to be reduced by certain therapies[3]; it should be assessed before initiation of treatment in all patients. NPTs produce a multitude of growth factors whose precise role remains to be ascertained. At present a huge effort is being made to explore alterations in oncogenes and tumour suppressor genes, but the complexity of the alterations is puzzling and such work has not yet provided much clinical guidance.

The demonstration of somatostatin receptors in 80–90 per cent of neuroendocrine tumours has not only clarified the rationale for the therapeutic effect of somatostatin analogues, but has also led to octreotide scintigraphy. This is now both a routine diagnostic staging tool and a predictive test for sensitivity to treatment with presently available somatostatin analogues (octreotide, lanreotide, RC-160). Most of these analogues bind with high affinity to the somatostatin receptors sst2 and sst5, and with lower affinity to sst3 (of the sst1–5 receptors so far described)[4]. Another diagnostic improvement is positron emission tomography (PET) for *in vivo* studies of metabolism in NPTs. The serotonin precursor 5-hydroxytryptophan is taken up by the tumours and PET can localize small lesions that are not detected by any other radiological method, including octreotide scintigraphy. PET can also be used to monitor treatment effects[5].

Considering the surgical treatment of these lesions, whenever possible curative resection should be aimed for, even at the stage of limited liver metastases. A peculiarity of NPTs is their relatively high rate of resectability compared with their exocrine counterparts. Unfortunately, there are no controlled randomized trials so far to show benefit from active surgery, although a non-randomized trial from the National Institutes of Health in the USA suggests that surgery alters the natural history of gastrinomas[6]. Good results from medical treatment have encouraged surgeons toward a more active approach and, even if radical surgery cannot be performed, debulking procedures should be considered. Small series describing liver transplantation in patients with NPTs have been published but the indication for such management requires to be evaluated in future studies. As most patients have the bulk of the tumour load in the liver, measures to reduce the arterial blood supply to the metastases may be applied. Nowadays, embolization with starch powder is used more often than arterial ligation. Liver embolization produces a biochemical response, with or without regression of metastases, in about 50 per cent of patients over a median duration of 10–15 months[7]. The exact role and timing of liver embolization has not been established.

From a chemotherapeutic point of view, combinations of streptozocin with 5-fluorouracil or doxorubicin can produce partial remission with a median duration of response of about 2 years in 40–60 per cent of patients with NPTs and is still first-line treatment in this patient category, for both functioning and non-functioning tumours[8]. In the subset of anaplastic tumours the combination of cisplatinum and etoposide produced remarkable remissions in 67 per cent of patients in a trial performed at the Mayo Clinic.

α-Interferons (IFNs) were introduced in the treatment of carcinoid tumours by the authors' group in 1982 because of their ability to stimulate natural killer cell function and to control hormone secretion, clinical symptoms and tumour growth. IFN is now registered in most European countries for the treatment of carcinoid tumours. The biochemical response rate in NPTs with moderate doses of IFN (3–6 mega units given between three and seven times a week) is about 50 per cent; significant tumour reduction occurs in only 15 per cent, but tumour stabilization occurs in approximately 80 per cent of patients over a median duration of response of 20 months[8]. In addition to stimulating the immune system, IFN is known to inhibit the cell cycle, to inhibit the production of growth factors and receptors secreted by the tumours, and to have antiangiogenetic effects (an effect that has been exploited in haemangiomas).

Somatostatin analogues have become increasingly important in treating neuroendocrine gastrointestinal tumours; the most commonly used analogue, octreotide, is registered in most countries for treatment of patients with vasoactive intestinal peptide- and glucagon-producing tumours. Summarizing the results reported in the literature to date, standard doses of octreotide (50–500 µg two or three times a day subcutaneously) produce symptomatic and biochemical responses in 30–75 per cent of patients over a median duration of 12 months[9]. Both of these effects appear to be dose dependent. Since the response varies markedly among individual patients (possibly due to patient-to-patient variation in the relative abundance of high- and low-affinity receptors expressed on the tumour cell membrane) it is important to titrate the dose of octreotide until adequate symptom and biochemical control is achieved. One must be cautious when treating insulinomas, since hypoglycaemia may increase. Significant reduction in tumour size occurs in only 5–15 per cent of patients, but stabilization can be obtained in 35–50 per cent. Both the biochemical and antiproliferative effects of octreotide, lanreotide and RC-160 are considered to be mediated by sst2 via stimulation of tyrosine phosphatases.

Trials with high-dose somatostatin analogue treatment (dosage greater than 3000 µg per day) for patients failing on standard octreotide treatment have produced symptomatic and biochemical responses in more than 50 per cent of patients, and a tumour size response in 11 per cent. The present authors have also shown that high-dose treatment induces apoptosis in these tumours, possibly mediated by sst3. Recently, slow-release formulations have been developed (Sandostatin-LAR (Novartis, Basel, Switzerland), lanreotide-PR) for administration intramuscularly every 2–4 weeks, which obviates the inconvenience of multiple daily injections. In one study using a validated European Organisation for Research on Treatment of Cancer instrument, several quality-of-life aspects were improved[10]. Somatostatin analogues have also been combined with IFN. In a group of 16 patients, who had become resistant to these analogues and other therapeutics, the addition of IFN (5 mega units given three times a week) to standard doses of somatostatin analogues resulted in a biochemical response[10] and a significant tumour reduction in three patients.

Neuroendocrine gastrointestinal tumours have traditionally been considered to be radioresistant. Recently, however, radiolabelled somatostatin analogues have been developed for therapeutic use. ^{111}In-labelled octreotide produced some subjective and biochemical responses and stabilization of tumour growth in patients with lesions showing high-grade uptake. Currently, other potential isotopes (e.g. ^{90}Y) are being investigated in phase I and phase II trials; these will deliver higher radiation doses to the tumours.

In conclusion, several therapeutic options are now available for patients with inoperable metastatic NPTs. By using a multimodal approach, applying different modalities synchronously or metachronously, the survival rates have improved. Even by 1993 patients with liver metastases had a median survival from diagnosis of 72 months, and a median survival from the start of medical treatment of 50 months (functioning 60 months *versus* non-functioning 40 months; $P = 0{\cdot}067$)[8]. With the availability of recently developed new therapeutic modalities, survival rates are improving; this is also true of quality of life, which is important in palliative care. Since a multidisciplinary approach is warranted, patients should be evaluated and treated in centres providing competence not only in surgery and endocrinology–gastroenterology, but also in oncology and radiology–nuclear medicine. It is likely that in such centres research in tumour biology, improved diagnostics and therapeutics will be performed concomitantly. Increasing knowledge of molecular genetics and tumour biology will in the future yield new therapeutics, subtype-specific somatostatin analogues, gene therapy and agents that can specifically block the intranuclear processes responsible for tumour development and progression.

Acknowledgements

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Announcement

The Scientific Committee of the Association of Surgeons of Great Britain and Ireland met on 25 November 1999 and considered the eight papers published as part of the special Association issue of the Journal (October 1999). It was judged that the paper entitled 'Emerging trends in the management of the impalpable testis' by M. E. Flett, P. F. Jones and G. G. Youngson was the winner of the BJS prize.

What should surgeons write?

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George Bernard Shaw, writing on education, quipped that 'those that can do; those that cannot teach', to which an aggrieved headmaster added 'and those that can neither do nor teach, write'. While this exchange may hold a kernel of truth, it cannot apply to surgeons since, of all the disparate disciplines of medicine, surgeons are the doers, the interventionalists and the technicians. We have learnt our craft by apprenticeship and by study of the rich library of surgical knowledge that has been handed down by previous generations. Surgeons are therefore not just doers but also teachers and writers. The challenge today is how to maintain this ethos of doing, teaching and writing at a time of rapid technological change, electronic communication and multimedia presentation.

The question 'What should I write?' is often asked by a basic surgical trainee of a senior colleague when it is realized that career advancement dictates a minimum level of academic achievement, best measured by published work. It can be a daunting challenge for, in order to write, one must have something to say. Frequently, the first stimulus for a young surgeon is an interesting patient who has prompted a literature search and perhaps a presentation to a local meeting. Many esteemed surgical writers, even journal editors, began a literary career with a time honoured case report[1]. Sadly, pressure of space and editorial policies directed at enhancing the impact factor of individual journals have reduced the opportunities for publication of case reports. None the less an interesting case report is a good start. An original observation, such as that of an unusual incidence of mandibular tumours in Ugandan children, reported in 1958 in the *BJS* by Denis Burkitt[2], can lead to important discoveries and a lifetime of research.

The opportunity to review an individual unit or institutional experience of a particular condition or surgical procedure frequently presents during surgical training and is often the next step in surgical writing to follow publication of a case report[3]. The exercise is important since it can provide insight into the process and difficulties of surgical audit. Such retrospective data are more often of local interest but sometimes are of national or international importance and worthy of publication. Editors, guided by the peer review process, will require evidence of the importance of such data, often asking 'Is there anything new here?' There is an increasing wariness on the part of editors of institutional databases that can be looked at in many ways and on many occasions. This is not to say that prospective and occasionally retrospective audit is not useful in moulding clinical practice. 'Salami slicing' of data is, however, to be discouraged; one good paper in a prestigious journal is worth many lesser publications. The concept of dividing a body of work into a large number of 'least publishable units' is to be discouraged.

Technical innovation is always a topic of interest and the evolution of surgical technique depends much on individual ingenuity and perseverance. The extraordinary story of Edoardo Bassini, his revolutionary treatment of inguinal hernia[4] and subsequent description of his technique[5] exemplify surgical innovation, illustration and writing. More recently, descriptions of novel techniques such as fashioning an ileostomy[6], carotid reconstruction[7] and laparoscopic cholecystectomy[8] are examples that have universally changed surgical practice. While most surgeons are from time to time tempted to cry 'eureka', few are blessed with the inspiration that leads to useful clinical application. However, most surgical journals will consider short reports of technical interest.

Surgical science takes as its foundation the formulation of a surgically relevant hypothesis that is tested in an experimental model. The majority of surgeons in training in the UK will undertake some period of formal laboratory or clinical research. This process, often in pursuance of a higher degree, can be a rich source of academic presentation and publication. A successful research project starts with a well written experimental protocol that in turn provides a footplate on which to build subsequent scientific manuscripts. Publication is an integral part of the experimental process which permits peer review and external recognition.

A typical period of research may present opportunities to publish a new methodology, results of animal or clinical experiments and possibly a review article. It is in this period of training that most surgeons learn the discipline of surgical writing from a research supervisor or consultant colleague. Those in fortunate positions will have as their academic supervisor a colleague with a keen sense of how and what to write. Others have to learn the discipline from the sometimes harsh rigours of the review process, or the sweeping changes required by an editor at the point of red pen.

Presentation to a scientific meeting is the usual prelude to a scientific manuscript. The peer review process for abstract selection and constructive interchange with others of similar research interest allows selection of appropriate material for publication and facilitates discussion in the subsequent manuscript. The fact that there are many times more abstracts published than original articles illustrates how difficult it is to complete this process and how rigorous peer review can be. Because of this, prominent surgical journals, *BJS* included, attach particular importance to original articles emanating from certain surgical and scientific meetings, e.g. The Association of Surgeons of Great Britain and Ireland and The Surgical Research Society. Support of the British Journal of Surgery Society for this process is evidenced by sponsorship of British Journal of Surgery prizes at meetings of affiliated surgical societies.

The outcome of a basic laboratory or clinical experiment may justify observation in a prospective clinical study and ultimately scrutiny in a randomized clinical trial. The importance of this process is evident from the prominence given by the *BJS* and other journals to randomized clinical trials. The emergence of evidence-based medicine as a discipline, the compilation of clinical trial information by the Cochrane collaboration, and the fact that decisions concerning Government funding of clinical practice are guided by the Audit Commission, highlight the need for surgeons to be intimately involved in the scientific scrutiny that is now being applied to the discipline of surgery. Organization of a randomized clinical trial is usually possible only in a large academic institution or national or international organization, but participation in multicentre trials is within the competence of most surgical units. In this situation, surgeons must be part of the scientific process of hypothesis generation, data collection, and analysis and publication. It is the latter elements of the process which are most easily delegated, but only surgeons should analyse and discuss that which is relevant to clinical surgery and not leave the reporting to others.

Review articles are an important part of the surgical literature occupying a middle ground between active research and established text. The relatively short time to publication of a journal review compared with a book chapter allows current literature to be compiled and interpreted in a manner that serves to educate and update the journal readership. More and more often today, systematic review articles and meta-analyses are being written by other (non-surgeon) professionals. Surgeons should not neglect this part of their scientific responsibility, the importance of which is evident from the prominence accorded to review articles in the *BJS* and other journals.

Topical or contentious issues in surgery may be dealt with in an editorial or leading article. These are usually written by invitation and place a burden of responsibility on the writer to review a subject objectively in a concise and impartial manner, ending with a conclusion that the reader can feel has the imprimatur of the journal's editorial board. An opportunity to write a leading article is not commonly afforded to a surgeon in training; nevertheless, a letter to the editor allows an opinion on recently published work or current issues to be aired.

The emergence of electronic publishing and CD-ROM text may change the medium in which book chapters and review articles appear. The possibility of including multimedia examples of surgical technique greatly enhances educational value, but these changes will not alter the essential need that surgeons have for ready access to up-to-date textbooks and detailed subspecialty reviews. Indeed, all practising surgeons will have a number of favourite texts to which they will occasionally revert. Some such texts are excellent examples of the various styles of surgical writing; Baily and Love's *Short Textbook of Surgery*, Golliger's *Surgery of the Anus, Colon and Rectum*, Sabiston's *Textbook of Surgery* and Schwartz's *Principles of Surgery* are a few personal favourites. The complexity of modern surgery is such that monographs are few and most such texts are multiauthored. Nevertheless the skills and vigilance of the editor are usually sufficient to ensure uniformity of style and excellence of content. The opportunity to contribute to such texts is both a professional challenge and a privilege that should not be delegated except under strict supervision.

The writing of prose does not always transfer to scientific surgical writing. The essence of scientific writing is to distil the subject matter to its core and then, confident of the fundamental hypothesis, the author can expand to convince the readership of the case. The surgeon in training who poses the question 'What should I write?' faces a daunting challenge. There are many formats from which to chose. An impulse to write is a better start than a perceived need to write for career advancement. There is a discipline that has to be learnt and a style that has to evolve. Above all, write what you as a surgeon would want to read.

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ARTICLES SUBMITTED TO THE *BRITISH JOURNAL OF SURGERY* AND *WORLD JOURNAL OF SURGERY*

ARTICLE A

Preincisional intraparietal *versus* intravenous administration of single dose of ceftriaxone for the prophylaxis of surgical wound infection

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(Submitted to the *British Journal of Surgery* 13.1.99)

ARTICLE B

Comparison of preincisional intraparietal *versus* intravenous administration of single dose ceftriaxone for the prophylaxis of surgical wound infection in high risk patients: prospective study

Ioannis Petrakis, Constantin Gonianakis, Ioannis-Sofocles Vassilakis, Nicolaos Vrachassotakis, Aristidis Tsatsakis, Ioannis Vlachonikolis, George Chalkiadakis (Departments of General Surgery and Toxicology, General University Hospital of Herakleion, University of Crete, Greece)
Correspondence Ioannis E Petrakis, Via Roma 95 Vasanello (VT) 01030, Italy
(Submitted to the *World Journal of Surgery* 5.1.99)

Each letter of submission was signed only by Dr Ioannis Petrakis and stated 'I would like to inform you that this article is original and has not been submitted or published elsewhere; all authors consent for the publication of this article'. These articles were refereed and rejected by each journal The journals, by coincidence, used an identical referee who spotted the similarity between the two papers. To all intents and purposes the articles were the same and, although the types of operation in group A and group B differed slightly between the two submitted papers (their *Table 1*), the other results in *Tables 2–6* were exactly the same. Three of the four figures submitted to the *British Journal of Surgery* were identical to those submitted to the *World Journal of Surgery*.

The editor of the *British Journal of Surgery* wrote to all authors seeking clarification of this issue. Only one reply was obtained from Dr I. G Vlachonikolis, Associate Professor of Biostatistics and Epidemiology in the University of Crete. Dr Vlachonikolis, in his letter to the *British Journal of Surgery* dated 25 May 1999, stated 'I do not even know Dr Petrakis. I was responsible for the statistical analysis and evaluation of results and, jointly with Dr Chalkiadakis and Tsatsakis, for the design of the study. I was not responsible for carrying out the clinical and surgical work of this study' Dr Vlachonikolis was disconcerted and dismayed by this episode and apologized for not having closely followed the progress of the research. Despite a reminding letter dated 26 August 1999, no further response has been received from the other authors

Although the *British Journal of Surgery* and *World Journal of Surgery* did not publish this work (rejected on the advice of referees) the submission of near identical work to both journals caused unnecessary work for referees and editors The work was so near identical that this would come within the bounds of duplicate publication. The *British Journal of Surgery* will continue to signal such behaviour in its pages and contributes vigorously to COPE – the Committee on Publication Ethics. It is hoped that readers enjoy the new series of commissioned articles on the writing of surgical papers which will appear in the Journal throughout the year 2000; these will be accompanied by recommendations from COPE on the ethics of publication.

J. R. Farndon
Professor of Surgery
Joint Editor, British Journal of Surgery

Committee on Publication Ethics

GUIDELINES ON GOOD PUBLICATION PRACTICE

1 Study design and ethical approval

Definition

Good research should be well justified, well planned, appropriately designed, and ethically approved. To conduct research to a lower standard may constitute misconduct.

Action

1 Laboratory and clinical research should be driven by protocol; pilot studies should have a written rationale.
2 Research protocols should seek to answer specific questions, rather than just collect data.
3 Protocols must be carefully agreed by all contributors and collaborators, including, if appropriate, the participants.
4 The final protocol should form part of the research record.
5 Early agreement on the precise roles of the contributors and collaborators, and on matters of authorship and publication, is advised.
6 Statistical issues should be considered early in study design, including power calculations, to ensure there are neither too few nor too many participants.
7 Formal and documented ethical approval from an appropriately constituted research ethics committee is required for all studies involving people, medical records, and anonymized human tissues.
8 Use of human tissues in research should conform to the highest ethical standards, such as those recommended by the Nuffield Council on Bioethics.
9 Fully informed consent should always be sought. It may not always be possible, however, and in such circumstances, an appropriately constituted research ethics committee should decide if this is ethically acceptable.
10 When participants are unable to give fully informed consent, research should follow international guidelines, such as those of the Council for International Organizations of Medical Sciences (CIOMS).
11 Animal experiments require full compliance with local, national, ethical, and regulatory principles, and local licensing arrangements. International standards vary.
12 Formal supervision, usually the responsibility of the principal investigator, should be provided for all research projects: this must include quality control, and the frequent review and long term retention (may be up to 15 years) of all records and primary outputs.

2 Data analysis

Definition

Data should be appropriately analysed, but inappropriate analysis does not necessarily amount to misconduct. Fabrication and falsification of data do constitute misconduct.

Action

1 All sources and methods used to obtain and analyse data, including any electronic pre-processing, should be fully disclosed; detailed explanations should be provided for any exclusions.
2 Methods of analysis must be explained in detail, and referenced, if they are not in common use.
3 The *post hoc* analysis of subgroups is acceptable, as long as this is disclosed. Failure to disclose that the analysis was *post hoc* is unacceptable.
4 The discussion section of a paper should mention any issues of bias which have been considered, and explain how they have been dealt with in the design and interpretation of the study.

Other sections of these guidelines will appear in future issues. The full guidelines are available at www.publicationethics.org.uk.

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Clinical dilemma

The 'failed' embolectomy

In the Clinical Dilemma slot, the editors pose a question to an acknowledged expert in the field. In this issue we address a difficulty encountered at thromboembolectomy. A patient has presented with severe acute ischaemia of a leg and femoral embolectomy has been carried out. Excellent inflow has resulted and, although some material was removed from the infrainguinal vessels, back-bleeding has been poor and concern remains about ischaemia. How should one proceed? Professor Hans Myhre of Trondheim in Norway replies.

In situations of acute lower limb ischaemia, the following questions are critical. What is the likely diagnosis? How long has the ischaemia lasted? And how severe is the ischaemia of the extremity? If the patient has a known potential source of emboli (such as atrial fibrillation or recent myocardial infarction), had sudden onset of symptoms and is free from occlusive disease in the contralateral limb, it may reasonably be assumed that the nature of the problem is embolic. If, on the other hand, the symptoms are subacute, the patient has known atherosclerotic disease with previous intermittent claudication and atherosclerosis is obvious in the contralateral limb, the suspicion should be that the problem is caused by an acute thrombosis superimposed on atherosclerotic changes. The possibility of a thrombosed popliteal aneurysm must also be kept in mind; palpation of the contralateral popliteal pulse and ultrasonography may be helpful.

Although preoperative arteriography can be useful, it should be performed on a selective basis, mainly in patients with suspected acute thrombosis on pre-existing atheroma and in whom the ischaemia is not too severe. However, I do not believe that preoperative arteriography is indicated for all patients with acute lower limb ischaemia as such imaging often results in a needless delay in treatment. It is logical to carry out arteriography in many patients on the operating table and I shall assume that this has been the plan in the present case.

Initial embolectomy has failed and what happens next must be determined by on-table arteriographic findings (*Fig. 1*). An arteriogram is easily produced by injecting 20–30 ml of contrast agent through a soft catheter inserted through the arteriotomy into the superficial femoral artery. If this clearly demonstrates residual embolic material, a further attempt at balloon extraction may be worthwhile. If the problem seems to lie in the popliteal trifurcation area, direct embolectomy through an arteriotomy in the infrageniculate popliteal artery is advisable. This allows extraction of emboli from both the femoral and tibial vessels[1]. The popliteal artery, however, is generally a rather small vessel, and the arteriotomy site should be closed using a vein patch angioplasty (preferably with a portion of vein unlikely to be required for any future bypass surgery).

If, on the other hand, the angiogram suggests that the problem is thrombosis on pre-existing atheroma, rather than emboli, an attempt may be made at thrombolysis using, for example, recombinant tissue plasminogen activator at a dose of 5 mg[2]. This can be injected into the superficial femoral artery when made up in normal saline to a volume of about 20 ml. The vessel is then clamped and 20–30 min is allowed to elapse for lysis to occur. At this point further arteriography may be undertaken. If lysis is incomplete, the step may be repeated in the hope of achieving an improved result. If successful, further arteriography will generally reveal an underlying cause of ischaemia, such as an atherosclerotic obstruction of the femoral or popliteal artery. Such lesions may be treated immediately by balloon angioplasty if the surgeon is

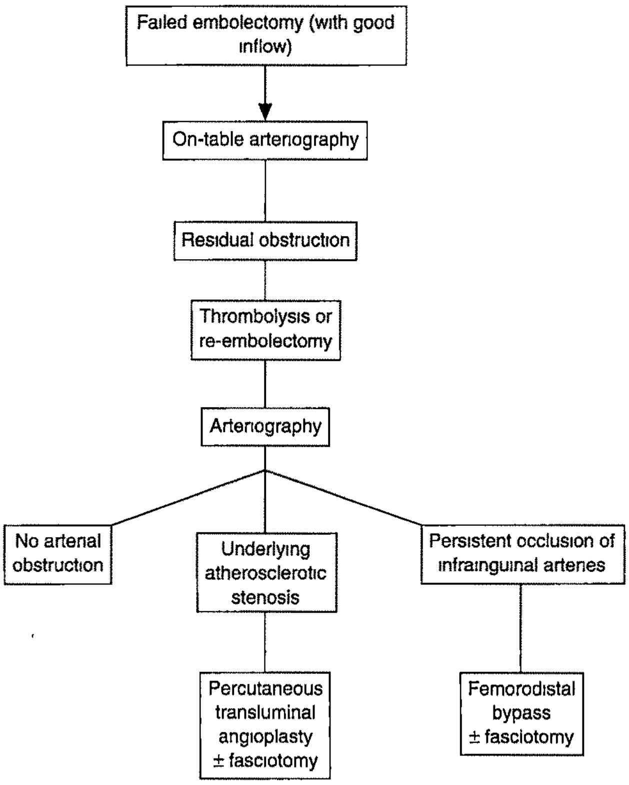
Failed embolectomy (with good inflow)
On-table arteriography
Residual obstruction
Thrombolysis or re-embolectomy
Arteriography
No arterial obstruction
Underlying atherosclerotic stenosis
Persistent occlusion of infrainguinal arteries
Percutaneous transluminal angioplasty ± fasciotomy
Femorodistal bypass ± fasciotomy

Fig. 1 Algorithm showing the steps for management of 'failed' embolectomy

experienced with the technique; otherwise direct reconstruction may be the solution.

If neither embolectomy nor thrombolysis has produced adequate patency and significant obstruction remains in the femoral or popliteal arteries, a bypass procedure may be considered. If arteriography through the superficial femoral artery has failed to demonstrate a satisfactory patent arterial segment in the distal part of the leg, an improved angiogram may be possible by injecting 20–30 ml of contrast agent directly into the profunda femoris vessel. Assuming a suitable outflow is identified, a vein bypass graft can then be created from the femoral artery to the popliteal or more distal arteries. If no distal vessel can be identified angiographically, it is probable that progressive thrombosis has occurred in the distal vessels and under such circumstances limb salvage is unlikely.

Following successful revascularization in a case such as this, there should be a low threshold for performing a fasciotomy. If the popliteal artery has been exposed below the knee, the incision can be prolonged medially and another incision made on the anterolateral side of the leg, opening all four fascial compartments. If the problem was caused by emboli, long-term anticoagulation is likely to be beneficial in all but the very elderly, and in those with a bleeding diathesis. In situations of thrombosis on pre-existing atheroma, it is likely that balloon angioplasty or bypass surgery will have been performed; long-term anticoagulation is unlikely to be indicated but antiplatelet therapy is justified.

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Review

Xenotransplantation

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Background: The success of clinical transplantation has led to a large discrepancy between donor organ availability and demand; considerable pressure exists to develop an alternative source of organs. The use of animal organs for donation is a possible solution that is not yet clinically applicable.
Methods and results: A literature review was performed based on a Medline search to find articles on xenotransplantation. Keywords included hyperacute, acute vascular, xenograft rejection combined with concordant and discordant. Additional references cited in these articles from journals not included in Medline were obtained from the British Library. Limited information on unpublished, preliminary work has been included from sources known to the authors, based on their research work in the field. One hundred and forty-six references and four personal communications have been included in this review article.
Conclusion: A greater understanding of the pathogenesis of xenograft rejection is developing rapidly. Strategies to abrogate hyperacute rejection have proved successful, but control of antibody-driven acute vascular rejection has not yet been achieved. The safety and viability of xenotransplantation as a therapeutic modality are still unproven.

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Introduction

The increasing success of allograft transplantation over the past 30 years has established this as part of routine clinical practice. It is the therapy of choice for end-stage organ failure. The growing number of people added to transplantation waiting lists worldwide has not been matched by a sufficient rise in the number of transplant operations performed[1]. This is because of a lack of adequate numbers of donor organs rather than any failure to provide sufficient transplantation facilities[2]. Even if all potential organ donors were identified and utilized, there would still be a substantial shortfall in the availability of donor organs. Various strategies including the use of 'marginal' organs[3], the use of non-heart-beating donors and using either biomechanical or non-human organs are being explored as potential solutions to this shortfall.

Xenotransplantation is defined as the transplantation of tissue between different species. Successful xenotransplantation would offer a real solution to the growing disparity between the demand for transplantable organs and the supply[4–7]. As well as increasing the supply of organs, this might enable recipient-specific genetic manipulation of the donor organ in order to reduce the need for long-term immunosuppression and the associated side-effects.

History of clinical xenotransplantation

Almost 100 years ago, well before the dawn of clinical allotransplantation, there were reports of the transplantation of animal tissues into human recipients with organ failure. In 1905, Princeteau[8] in France implanted slices of rabbit kidney into a uraemic child. He claimed improvement of renal function before the child's death from pneumonia.

In the 1960s some success was obtained in a human recipient of a renal transplant from a chimpanzee as part of a series of xenotransplantation procedures performed by Reemtsma *et al.*[9]. Azathioprine, actinomycin-C and corticosteroid immunosuppression was used before and after transplantation, in combination with local irradiation of the organ. The patient survived for 9 months. Histology of the graft at post-mortem examination showed a vascular-based rejection process, although the cause of death was primarily related to infection rather than renal failure.

In the precyclosporin era, Starzl *et al.*[10] achieved 70-day survival in one patient who received an orthotopic baboon liver. This patient died from overwhelming sepsis with little histological evidence of rejection in the graft at autopsy. In a much publicized case, Bailey *et al.*[11,12] in 1984 performed orthotopic transplantation of a baboon heart that functioned for 20 days in a human neonate born with a hypoplastic left ventricle. In spite of immunosuppressive treatment, including cyclosporin, terminal histology showed that graft failure was due to a vascular rejection process. More recently a number of diabetic patients in Sweden have undergone fetal pig to human islet transplantation. Although there was evidence of prolonged production of porcine insulin and cell survival, this did not lead to a reduction in exogenous insulin requirements.

The only current clinical xenotransplantation trial involves the implantation of dopaminergic porcine fetal neural cells to treat diseases of the basal ganglia[13]. The presumed immunological privilege afforded to engrafted cells by the blood–brain barrier, combined with the absence of vascular endothelium compared with a solid organ, is thought to provide some protection from rejection. The initial results of these experiments are encouraging, with positron emission tomography demonstrating functional transplanted cells and a reduction in drug requirements in some cases.

The longest surviving xenografts in human recipients have occurred where species phylogenetically close to man (old world monkeys or great apes) have been used as organ donors. In grafting between species, not necessarily just to human recipients, different patterns of rejection are noted. In 1970 Calne[14] suggested two different categories of xenograft based on the observation of different rates of rejection. The term concordant xenograft is applied to grafts between species that are rejected in a time frame similar to that of transplantation into an unsensitized recipient (first set response). This would occur, for example, if a baboon or chimpanzee organ were to be transplanted into a human recipient. The term discordant xenograft is applied to primary grafts between different species that undergo hyperacute rejection (HAR), as is observed when an allograft is transplanted into a sensitized recipient (second set response). HAR is characterized by microvascular thrombosis and interstitial haemorrhage leading to immediate graft destruction without graft function. It is associated with the presence of preformed antispecies antibodies and complement activation. Transplantation of a pig organ into a human recipient is an example of discordant combination.

Issues in xenotransplantation

Choice of donor species

With respect to immunological compatibility, a concordant species combination poses fewer problems than a discordant combination. However, there are serious objections to the use of non-human primates for clinical xenotransplantation. First, the evidence of a high level of social development and intelligence among non-human primates makes their use as donors ethically and culturally unacceptable to many people. More specifically, primate organs comparable in size to adult human organs can only be obtained from endangered species; this greatly limits the capacity of concordant xenotransplantation to alleviate the shortage of donor organs[15]. Furthermore, the captive rearing of primates is slow and expensive in comparison to that of domestic farm animals. The question of zoonotic disease transmission is considered in a later section.

Much research investment has now been directed to the pig as a potential donor species. Many cultures accept the breeding of pigs for domestic use and so their use as potential organ donors is more acceptable. Pigs breed quickly in captivity and produce large litters that would enable supply to meet the demand if discordant transplantation became a realistic clinical therapy. A wealth of experience exists in commercial pig breeding, which would be invaluable in the production of specific pathogen-free animals.

Immunological barriers

When a solid organ is transplanted between discordant species, a vigorous, largely humoral, immune response occurs on reperfusion; this results in microvascular thrombosis and interstitial haemorrhage. If this occurs without evidence of graft function it is termed HAR. Experimentally, the prevention of HAR in discordant solid organ xenotransplantation has come about by understanding the pathological and immunological processes involved. Three important components have been identified: complement[16–20], xenoreactive antibodies[7,21–27] and endothelial cell activation[16,28–32].

In HAR the major target of preformed xenoreactive natural antibodies is the galactosyl α-1,3-galactose (Galα1–3Gal) sugar residue[33–35], which is present on the endothelial and other cell types of lower mammals and new world monkeys. In humans, over 80 per cent of the preformed complement-fixing antispecies antibodies are directed against the Galα1–3Gal epitope[26,36].

Galα1–3Gal is synthesized by α-1,3 galactosyltransferase, which catalyses the addition of a terminal α-linked galactose to *N*-acetyl lactosamine. Evolutionary genetic deletions and substitutions have produced a pseudogene for the transferase in old world monkeys and humans. These species lack the α-Gal residue on cell surfaces and also have circulating antibodies against it. There is considerable amino acid sequence homology between the pig α-1,3 galactosyltransferase and human ABO blood group transferases which may be evidence of a common evolutionary origin. The existence of preformed anti-αGal antibodies probably reflects evolutionary differences between species in the basic immune defence mechanisms against bacterial pathogens, in particular the response to normal gut flora[37–40].

Complement fixation by bound xenoreactive antibody generates C3a, C5a and membrane attack complex (MAC, C_{5b-9}) via the classical pathway. There is evidence in small animal models that HAR can also be caused by complement activation by the alternative pathway, without the binding of xenoreactive antibodies[41]. However, in pig to primate discordant transplantation the removal of xenoreactive antibodies prevents HAR[26,39–42]; this is evidence that in this species combination the alternative pathway alone is insufficient to cause HAR.

The antibody deposited within the graft increases the migration, recruitment and activation of Fc receptor-bearing leucocytes. Anaphylotoxins, histamine and serotonin generated induce surface platelet activating factor (PAF) and early-phase cytokine expression. Resultant endothelial cell contraction and retraction expose the underlying basement membrane. Platelet activation occurs on contact with the extracellular matrix and the generation of complement factors (C_{5b-9}, C3a and C5a). A variety of signals are generated that cause the loss of heparan sulphate[43,44] and ecto-adenosine 5′-diphosphatase (ecto-ADPase)[29,32,45,46] from the endothelial surface. These are natural anticoagulants and their loss predisposes to microthrombus formation with associated fibrin deposition[47]. As a consequence of these events, thrombosis of the microvasculature occurs with interstitial haemorrhage.

If HAR is abrogated, discordant and concordant xenografts behave in a more similar manner, and are rejected by a continued humoral process over a longer time scale. This is termed acute vascular rejection (AVR). Macroscopically, rejected grafts show purple discoloration with vascular congestion and parenchymal haemorrhage. Histologically, there is a higher degree of intravascular thrombosis and less haemorrhage than with HAR[48,49]. In general, there is a relative sparsity of cellular infiltration compared with allograft rejection[50]. Immunosuppression can go some way to delaying the time to graft failure, but higher doses of therapy are required than in allotransplantation[51–53].

Complement and antibody depositions are again immunohistochemical features, with increased levels of cytokines, adhesion molecules and procoagulants generated by endothelial cell activation. Continued antibody deposition is thought to play a central role in AVR[54,55]; the onset of AVR correlates with the reappearance of antidonor antibodies. Unlike HAR, isotypes of immunoglobulin (Ig) G antibodies are as effective as IgM in causing AVR[56]. The elicited rather than the preformed antibody response is more important in the aetiology of AVR[57]. A variable degree of mononuclear cell infiltration is also seen[58]. These appear to be activated monocytes and natural killer (NK) cells, but the exact immunophenotype of these cells has been elusive[59–63]. NK cells interact with antibody to produce an antibody-dependent cell-mediated cytotoxicity, as well as direct and indirect endothelial cell activation.

HAR is associated with endothelial cell activation that does not involve gene activation or protein synthesis[5,64,65]. This is termed type 1 endothelial cell activation. Endothelial cell processes dependent on gene upregulation and protein synthesis are described as type 2 endothelial cell activation. Type 2 endothelial cell activation, which occurs in AVR, produces two major effects that result from activation of NF-κB transcription[31,66]. NF-κB is a transcriptional activator associated with immediate early gene expression. The first causes endothelial cells so stimulated to express adhesion molecules (i.e. E-selectin, vascular cell adhesion molecule-1 (CD106), intercellular adhesion molecule-1 (CD54)) and cytokines (interleukin (IL) 1, IL-6, IL-8). These surface configurational changes upregulate T helper lymphocytes. Adenoviral transfection producing inhibition of endothelial cell activation by the expression of antiapoptotic genes, such as *haemoxygenase 1*, *A 20* and *bcl2*, may protect the endothelium from antibody-mediated damage[67–71]. This is currently an area of great investigative activity as it is hoped that a period of protection will allow graft ‘accommodation’ to occur[30,72–74].

The second change is to alter the balance of thrombomodulators and generate the procoagulant state that leads to intravascular thrombosis[75]. There is evidence that a species-specific regulation of the coagulation cascade exists[66]. Porcine endothelial cell-derived tissue factor pathway inhibitor does not act upon human factor Xa to prevent thrombosis as efficiently as its human equivalent. As a result of the endothelial cell activation coagulants, including PAF and tissue factor, are generated.

Vascularized discordant xenografts are usually destroyed by HAR or AVR and so little is known about the cellular response to xenografts[59,76]. *In vitro* and small animal concordant models show evidence of a process similar to chronic allograft rejection[48,77–80]. In these experiments, engrafted tissues show some interstitial fibrosis, with arterial intimal thickening and infiltration with major histocompatibility complex class II-positive, CD4-positive macrophages[48,78].

Porcine cartilage xenografts, explanted from cynomolgus monkeys 2 months after transplantation, contain extensive mononuclear cell infiltration[81]. The vast majority of the cells are either T cells or macrophages. These animals have a large increase in anti-Gal antibody activity after transplantation. The elicited anti-Gal antibodies are not only of very high titre but also of greatly increased affinity. When porcine cartilage treated with coffee bean α-galactosidase is engrafted (this cartilage is free of any α-Gal epitopes) no increase in anti-Gal antibodies is noted. These grafts at similar intervals after transplantation show much less cellular infiltration, made up mainly of macrophages and very few T cells. Much of the cellular response to discordant xenografts may be antibody-dependent cell cytotoxicity. Depletion of α-Gal epitopes also reduces endothelial cell activation in these chronically rejected grafts[82]. Of note is that similar antibody response patterns to α-Gal are found in the blood of diabetic patients treated with cultured fetal pancreatic islet cells[83].

Physiological barriers

There is evidence that some proteins and hormones may be species specific and may not regulate human systems appropriately. A successful xenograft would ideally perform the homoeostatic and hormonal functions as effectively as an allograft. Intuition suggests that organs from concordant species are more likely to control human metabolism than those from discordant species[84,85]. This is supported by the experience in Pittsburgh with baboon to human liver transplantation in which most metabolic functions of a human liver are provided effectively by the graft, including synthesis of proteins that are functionally active for over 2 months[10].

The lower degree of protein sequence homology makes it less likely that hormones from discordant species will regulate human systems adequately[86]. In the authors' experience the successful discordant xenotransplantation of a life-supporting transgenic pig kidney into a cynomolgus monkey recipient is associated with anaemia that may be abrogated by exogenous recombinant human erythropoietin[87].

When pigs of weights equal to those of adult human recipients are examined, their organs are found to be of comparable weight and volume[88,89]. Preliminary studies from the authors' group suggest that cardiovascular parameters (including blood pressure, cardiac output and left ventricular stroke work) for adult human-sized pigs are similar to those for adult humans (personal communication, D.J. Ostlie).

Risk of zoonotic disease

The potential for zoonotic infection is an issue of concern[88]. Many pathogens that are known to cross the species barrier can be readily screened and donors selected on this basis. Some pathogens transferred from the donor that cause disease in allograft recipients, such as cytomegalovirus and some hepatitis viruses, are species restricted[90–92]. Some primate diseases such as simian Herpes B and the retroviral infection, simian immunodeficiency virus, are known human zoonoses that are lethal.

Man has coexisted in close proximity to domesticated animals for centuries. This might suggest that major zoonotic infection should be less likely from pigs than non-human primates[35]. However, porcine endogenous retroviruses (PERVs) have recently been shown to infect cultured human cell lines[93,94]. These retroviruses are incorporated in the porcine genome and so cannot readily be eradicated. Two groups reported on the infectious capacity of these viruses in 1998. In one study of ten diabetic patients transplanted with porcine islets, polymerase chain reaction (PCR) analysis was used to detect PERV-related sequences in the patients' blood cells[95]. In all cases PCR analysis showed no evidence of patient infection. Patience *et al.*[93], in a study of two patients undergoing extracorporeal porcine kidney perfusion, found no evidence of retroviral infection at up to 36 months' follow-up.

Within the past few months the largest study published to date, following 160 patients with some form of xenoperfusion or transplantation, has found no detectable PERV infection at up to 12 years' follow-up[96]. A degree of microchimerism was noted in 23 patients, although there was no evidence of clinical or subclinical infection related to this finding.

Strategies to prolong experimental xenograft survival

Complement inhibition

HAR requires activation of the complement cascade. The normal physiological control of complement activation includes membrane bound proteins, regulators of complement activity[97] and also fluid-phase inhibitors including factors I and H (*Fig. 1*). In general, regulators of complement activity are largely species specific and limit the action of their own complement better than that of other species[98,99]. The development of transgenic pig lines expressing human regulators, such as decay accelerating

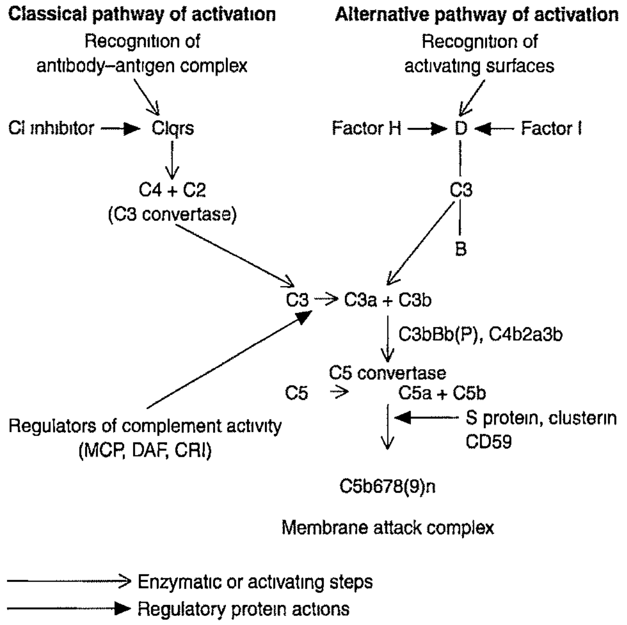
Classical pathway of activation
Recognition of antibody–antigen complex
Alternative pathway of activation
Recognition of activating surfaces
Cl inhibitor
Clqrs
Factor H
D
Factor I
C4 + C2
(C3 convertase)
C3
B
C3 → C3a + C3b
C3bBb(P), C4b2a3b
C5 convertase
C5 → C5a + C5b
S protein, clusterin
CD59
Regulators of complement activity
(MCP, DAF, CRI)
C5b678(9)n
Membrane attack complex
Enzymatic or activating steps
Regulatory protein actions

Fig. 1 Complement cascade and sites of regulation. MCP, membrane cofactor protein, DAF, decay accelerating factor; CR1, complement receptor 1

factor (DAF, CD55)[21,100–106], membrane cofactor protein (MCP, CD46) and CD59, has produced discordant organs very largely protected from HAR. Complement inhibition, using cobra venom factor or soluble complement inhibitors, also prevents HAR in discordant models of xenotransplantation[107,108]. Some inborn deficiencies that prevent MAC (C_{5b-9}) formation can also prevent the occurrence of HAR[109]. The terminal complex appears critical in producing breaches in the integrity of the endothelium, with extravasion of vascular contents and platelet adhesion.

Removal of xenoreactive antibody

Plasmapharesis or passive immunoadsorption on columns can be used to prevent HAR by reducing circulating xenoreactive natural antibodies[110–115]. Such columns comprise small spheres coated with covalently bound α-Gal which extract the anti-αGal antibodies before the plasma is returned to the recipient. However, discontinuation of the therapy leads to a rapid return of xenoreactive antibodies and subsequent rejection. It is IgM binding in particular that is important in HAR[116]. Infusion with human IgG into pig to primate heart transplant recipients has been shown paradoxically to prolong organ function and survival, possibly owing to antagonism between idiotypes[117].

Cyclophosphamide

The most efficacious agent in delaying AVR to date has been cyclophosphamide[118]. It has proved crucial in models of pig to non-human primate renal and cardiac transplantation. Cyclophosphamide is cytotoxic to B cells but may also reduce type 2 endothelial cell activation. It has been used both as induction and maintenance therapy but, although effective, it has well recognized side-effects. Other immunosuppressive agents have also been tried including cyclosporin, rapamycin and analogues, and mycophenalate and its derivatives.

Splenectomy

Splenectomy at the time of xenograft implantation reduces the frequency and severity of rejection episodes as well as increasing the overall survival of recipients[87,119–121].

Alteration of α-Gal expression on endothelial cells

Genetic manipulations to reduce the number of α-Gal epitopes on the endothelial cell surface by the overexpression of α-1,2 fucosyltransferase have also been used[122–126] with limited success. Gene deletion (knockout) techniques have been used to produce α-Gal epitope knockout mice. These mice do not express the α-Gal epitope on cell surfaces[127,128]. However, they express other immunogenic epitopes on the endothelial cells against which preformed human xenoreactive natural antibodies have been detected. Despite this, the concept of an α-Gal epitope free porcine donor is still attractive as a solution to the immunological problems of discordant xenotransplantation to many investigators. Thus, considerable efforts are currently being directed at developing α-Gal knockout pigs.

Other experimental approaches

In order to limit the endothelial cell activation seen in AVR, work with *in vitro* porcine and *in vivo* rodent models has been undertaken to produce NF-κB pathway blockade by genetic manipulation[129]. Some promising early results have been achieved. The same group are attempting to use viral transfection models to alter some of the tissue factor- and ecto-ADPase-dependent pathways.

Accommodation[130,131] is a phenomenon that occurs when antibody and/or complement are temporarily depleted in a recipient of an incompatible graft, but with continued graft function after the return of these components to the recipient's circulation. It was first observed in recipients of ABO-incompatible kidneys and has also been found in recipients with circulating antidonor human leucocyte antigen antibodies. It is postulated that accommodation might occur in recipients of vascularized xenografts. Endothelial cells stimulated at a low level, insufficient to induce type 2 activation, show increased expression of antiapoptotic genes and inhibition of NF-κB transcriptional activation. The biological basis of this process is unclear. Possible mechanisms include: (1) changes in the stimulation provided by the engrafted tissue; (2) a reduction of the recipient's ability to react; and (3) an increase in the levels of protective endothelial cell-derived components, such as DAF. Undoubtedly it would be beneficial if accommodation could be induced in xenograft recipients.

Tolerance is a systemic immunological state in which the antigens of the donor are regarded as 'self' and therefore do not induce an immune response[129,132–134]. This state coexists with otherwise normal recipient immunocompetence[135]. This has been induced experimentally by sublethal irradiation[136,137], and non-depleting peripheral T cell blockade[138] with monoclonal antibodies[139] followed by donor and recipient bone marrow transplantation[140–144], leading to bone marrow chimerism[145]. Some investigators have used engraftment of thymic tissue to induce a donor-specific tolerant state in the recipient[146]. Antileucocyte antibodies and approaches to generate chimeric donor/recipient cells may allow tolerance without such toxic therapy.

Experimental results

In concordant models, considerable success has been obtained with prolonged graft survival without the use of transgenic donors. Hamster hearts transplanted into rats (a concordant combination) do not encounter HAR, but they are rejected within 3–4 days as xenoreactive antibody titres rise rapidly to levels that elicit a classical antibody- and complement-mediated acute xenograft rejection[76]. This can be blocked by a combination of immunosuppressive agents (leflunomide and cyclosporin), prolonging survival for up to 70 days. Survival of over 500 days in juvenile baboon recipients of orthotopic cardiac xenografts from rhesus monkey donors has been reported[147]; splenectomy with selection of donor and recipient for ABO compatibility combined with immunosuppression with FK 506 and methotrexate were employed. Similar survival has been achieved without splenectomy using cyclosporin instead of FK 506[147].

Limited success has been obtained in small animal discordant models. Prolongation of graft survival after heterotopic cardiac engraftment from guinea pigs to Lewis rats treated with either soluble complement inhibitor or cobra venom factor has been demonstrated[107]. The maximum mean graft survival was 69 h in animals treated with cobra venom factor, whereas unmodified controls rejected their grafts in a mean time of 15 min.

In models of pig to non-human primate xenotransplantation, the use of porcine organs transgenic for human regulators of complement activity leads to the reliable abrogation of HAR. After transplantation into baboons, hearts from transgenic pigs expressing human DAF and CD59 underwent AVR, leading to graft failure within 5 days[115]; the histology was characterized by endothelial injury and fibrin thrombi. Hearts from the transgenic pigs transplanted into baboons, in which circulating antibodies were depleted using anti-immunoglobulin columns, did not undergo AVR in five of six cases. The longest survivor died 29 days after operation from an infectious complication of immunosuppression. In one case, AVR of the xenograft occurred in a baboon in which the level of antidonor antibody rose after antibody depletion was discontinued.

The authors' group has recorded a maximum survival of 78 days for a life-supporting pig transgenic for human DAF to cynomolgus monkey renal xenograft, and a 39-day survival of an orthotopic cardiac xenograft from a human DAF pig to a baboon recipient. The grafts sustained the animals in a healthy state, with essentially normal organ function, until the recipients died from side-effects of the immunosuppressive regimens (E. Cozzi and C. Vial, personal communication).

Ex vivo perfusion of pig livers with human blood for periods of up to 3 days has demonstrated that the synthetic function, excretory function and metabolic regulation of measured variables are maintained throughout this period. This evidence suggests that a discordant xenograft liver could temporarily support a patient in fulminant hepatic failure on an extracorporeal circuit (M.J. Rees, personal communication).

The future for clinical xenotransplantation

It is possible that the initial clinical trials of xenotransplantation will involve patients in one of two groups. Cellular xenografts, particularly islet cells in the treatment of diabetes, are attractive candidate in that the consequences of immunological failure of the graft would be much less severe than in the case of a solid organ graft. The transplantation of neural cells, for example, in the treatment of Parkinson's disease, might also be considered in the same context.

The second group of patients comprises those for whom transplantation represents a life-saving procedure but who are extremely unlikely to receive this in the time available. The treatment of acute liver failure, possibly by temporary extracorporeal perfusion of a porcine liver, is one example of such a situation; many patients die while awaiting emergency liver transplantation and the xenogeneic liver might provide support for long enough to obtain a liver for transplantation. The temporary support of patients in cardiac failure awaiting transplantation, by means of an auxiliary cardiac xenotransplant, might also fall into this category.

A more complex issue is the introduction of xenotransplantation as an alternative to cardiac and renal allotransplantation, therapies of proven effectiveness. This may occur when certain prerequisites have been fulfilled. First, the introduction of xenotransplantation in the areas described above will provide vital data in relation to safety and immunological compatibility. Second, the demonstration of reliable medium- to long-term efficacy in appropriate preclinical animal models should predict the outcome of clinical trials and enable the first patients to be treated with at least a reasonable probability of benefit.

Elective xenotransplantation might enable the development of pretransplantation recipient therapies to induce tolerance. Undoubtedly, it would then provide a new supply of organs to overcome the ever-increasing donor deficit, thereby increasing the number of patients benefiting from transplantation.

As the possibility of clinical xenotransplantation approaches reality, it is important that the use of xenogeneic tissue should be closely regulated and monitored. The consequences for both patients and society must be considered very carefully.

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Review

Genetic predisposition to breast cancer: a surgical perspective

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Background: Molecular alterations in proto-oncogenes, tumour suppressor genes, and genes that function in DNA damage recognition and repair are considered to be hallmarks of a carcinogenic process, including breast carcinogenesis.

Methods: A computer-assisted search of the English literature (Medline database, 1990–1999) was performed, followed by a manual search of the reference list of pertinent articles retrieved.

Results: Hereditary breast cancer accounts for 5–10 per cent of all breast cancer cases. About 90 per cent of hereditary breast cancers involve mutation of the *BRCA1* and/or *BRCA2* genes. Other cancer-related genes (including *myc*, c-*erbB2*, *Tsg101* and *Mdgi*) are involved in breast carcinogenesis, but they do not give rise to familial breast cancer syndromes. Risk estimation is the most important clinical implication. Management options for the high-risk mutation carriers include cancer surveillance and preventive strategies (prophylactic surgery or chemoprevention).

Conclusion: Despite inadequate knowledge about the genetic predisposition to breast cancer and its clinical implications, the demand for genetic testing is likely to expand rapidly. In addition to risk estimation, cancer surveillance and preventive strategies, gene therapy offers a new and theoretically attractive approach to breast cancer management.

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Introduction

Breast cancer is the commonest neoplastic disease in women in the Western world, with a lifetime risk of 11–12 per cent in the general population[1–3]. In spite of earlier detection and better treatment, largely due to recent technological advances, it is still the second leading cause of cancer-related death, claiming 46 000 lives of women annually in the USA[1]. Various factors (including reproductive, environmental, endogenous factors such as the hormonal milieu as determined by pregnancy, menstrual changes and hormonal intake) are associated with breast cancer risk, but family history is the strongest known epidemiological risk factor. Epidemiological studies have indicated that there is a genetic predisposition to breast cancer; indeed 5–10 per cent (9000–18 000 cases per year in the USA) of women who develop breast cancer do so because of a heritable predisposition[4].

Progress has recently been made in defining some of the critical processes associated with breast carcinogenesis. It is generally accepted that malignant transformation involves genetic and epigenetic changes that derail common regulatory mechanisms and result in uncontrolled cellular proliferation and/or aberrant programmed cell death or apoptosis[5–8]. These abnormalities, hallmarks of a carcinogenic process, are frequently associated with molecular alterations in one of three broad categories of genes related to cancer development: proto-oncogenes, tumour suppressor genes and, most recently, genes that potentially function in DNA damage recognition and repair. Activation, inactivation or loss of function of these genes may be a result of genetic predisposition and/or exposure to physical (e.g. radiation), chemical (e.g. carcinogens, dietary components), biological (e.g. viruses) and other environmental factors[5–8]. However, the specific biochemical and molecular mechanisms underlying many of these complex carcinogenic events still remain to be elucidated. Understanding the cellular and molecular processes that drive normal human breast epithelial cells to neoplastic growth remains a major challenge for cancer biologists.

The rapid development of clinical cancer genetics means that it is increasingly important for those treating breast cancer to have an understanding of this field. Contemporary breast cancer therapy has evolved to a point at which a multidisciplinary approach is the standard of care for most patients with breast cancer, even those with early stage disease. The surgeon, traditionally having a primary coordinating role in breast cancer management, must have a firm grasp of the underlying theory and, more importantly, must understand clearly the promise and pitfalls that accompany this new information.

It is typically the surgeon who supplies initial information, advice and support to a person with breast cancer. Prophylactic surgery is an option in the management of mutation carriers. Mutation status may also be important in selection of the optimal method in the surgical management of affected mutation carriers (e.g. breast-conserving surgery *versus* mastectomy). For these reasons, the surgeon should be involved in the broader issues of oncology management for the patient with breast cancer (including molecular biology), or he or she will be relegated to a secondary and largely technical role in the treatment of this disease.

Multistep breast carcinogenesis

There is increasing evidence that alterations in cell cycle regulation may be a unifying feature of malignant transformation. Such alterations may enable unregulated cell growth and provide cells with a selective growth advantage[6–8]. Like all normal diploid and differentiated somatic cells, normal human breast epithelial cells have a limited capacity to divide both *in vivo* and *in vitro*. Cellular mortality of normal breast cells is characterized by a progressive cessation of cell growth manifested in cell culture by senescence that typically occurs after ten to 20 passages *in vitro* (approximately 100–200 population doublings)[9,10].

In contrast, transformed or tumour breast cells are able to escape from senescence, as a result of genetic or epigenetic changes that disrupt the regulatory mechanisms of limited growth potential, and are thereby considered immortal[11]. Induction of immortality (immortalization) involves abrogation of cellular programmes for limiting the rate and number of cell replication and is generally perceived as a key event of an oncogenic process[9–11]. Clonal expansion of the cell can lead to tumour progression as a result of successive genetic alterations, resulting in cellular transformation, loss of contact inhibition and the acquisition of invasive capacity. Molecular studies support the concept that multiple and cumulative genetic alterations are required for tumorigenesis[6].

Based upon histological evaluations, development of breast cancer has been postulated to be a multistep process and follows a defined sequence of qualitatively different events[12], as documented for a number of other malignancies[13–15]. Although not obligatory, many breast cancers appear to develop through a series of premalignant stages, defined as atypical hyperplasia and carcinoma *in situ*, leading to invasive cancer and ultimate metastasis[12,16]. However, breast tumour evolution does not always follow a simple linear progression model, but rather appears to involve a more complex process, characterized by simultaneous evolution of multiple independent tumour regions – a scenario probably responsible for the great heterogeneity witnessed in this disease.

The different phases of this complex phenomenon proceed through the progressive accumulation of multiple carcinogenic transformations[12,15,16]. This is supported by the increased risk of cancer for women with preneoplastic lesions[5], by the accumulation of genetic and phenotypic changes in cultured breast cells during immortalization, by the tumorigenic potential of transplanted cells with defined genetic modifications, and by the transgenic mouse models of breast cancer[17]. The disease, like other forms of cancer, is thought to progress through accumulation of genetic defects in oncogenes, tumour suppressor genes and mismatch repair gene, and through complex rearrangement of the genome[16,17].

Nowadays, the genetic heterogeneity of familial breast cancer is well recognized. Several specific gene loci involved in hereditary breast carcinogenesis have been identified (see below). However, in theoretical modelling, the majority (about 90 per cent) of familial breast cancers can be attributed to the high-penetrance genes *BRCA1* and *BRCA2*[17]; germline mutations of other 'cancer genes' are quite rare and so are unlikely to account for more than a minority of breast cancer cases.

Specific breast cancer predisposition genes

BRCA1

Molecular epidemiology

Mutations in *BRCA1* account for breast cancer in about 50 per cent of families with three or more cases of early onset breast cancer, hence the considerable interest in detecting mutation in that gene[4,18–20]. The lifetime risk of breast cancer in such women is estimated to be 87 per cent (82 per cent by age 70 years and 50 per cent by age 50 years)[4]. Recent studies of women who develop breast cancer at a very young age indicate that 13 per cent of those who are diagnosed with breast cancer under the age of 30 years, and 7 per cent of women who are diagnosed with breast cancer under the age of 35 years, have germline *BRCA1* alterations[21,22]. The cumulative risk of developing a second breast cancer was estimated to be 60–80 per cent for affected mutation carriers who live to the age of 70 years[23,24]. Additional studies indicate that *BRCA1* alterations are found in 76 per cent of breast cancer families with at least one case of ovarian cancer and in 92 per cent of families with two or more cases of ovarian cancer[25]. The lifetime risk of a woman with a *BRCA1* alteration developing ovarian cancer is estimated to be 40–50 per cent (23 per cent by age 50 years). These ranges should be compared with the general population lifetime risk for breast and ovarian cancer of 11–12 and 1·3 per cent respectively[26].

Of note, all breast cancer-related *BRCA1* mutations identified to date are germline mutations[27], which means they are present in all cells in the body, including eggs or sperm, and so can be passed on to the next generation. Acquired mutations, those that occur after birth in a single cell, are not passed on unless that cell happens to be a sperm or egg, but may give rise to cell clones that become cancerous. Acquired (somatic) *BRCA1* mutations are at the very least rare and possibly non-existent in human breast cancers; they are found only rarely (about 10 per cent) in human sporadic ovarian cancers[28,29]. This is in contrast to other classical tumour suppressor genes, mutations of which are frequently found in the sporadic counterparts of the familial cancers[6–8].

The incidence of germline *BRCA1*/*BRCA2* mutations is especially high among Jews and, in particular, Ashkenazi Jews (a genetically distinct population whose ancestors lived in central and eastern Europe)[30,31]. Indeed, the incidence of *BRCA1*/*BRCA2* alterations is as high as one in 40 to one in 50, accounting for approximately 50 per cent of early-onset breast cancer in Ashkenazi Jewish women[4,30]. This may explain, at least in part, the high risk of breast cancer in women in the Ashkenazi population. It has been calculated that 7·5 per cent of non-Jewish women and 38 per cent of Jewish women with breast cancer under the age of 30 years would be expected to have germline *BRCA1*/*BRCA2* mutations[32,33]. For women under 40 years who have breast cancer, the calculated attributable risks would be 5·3 and 27 per cent respectively.

Structure and function

BRCA1 is a large gene, encoding a messenger RNA (mRNA) of 7·5 kilobases (kb) (1865 amino acids)[34]. The entire genomic region encoding *BRCA1* spans over 100 kb and is composed of 24 exons, 22 of which encode for a protein 1863 amino acids long. One of these (exon 11) is particularly large. *BRCA1* is expressed during cellular proliferation and its function is necessary for cell proliferation and tissue differentiation. Recent research has suggested that the *BRCA1* protein may also have more specific roles in controlling the rate of cellular proliferation, ensuring the fidelity of DNA duplication, maintaining genome integrity and/or preventing the replication of damaged DNA[34,35].

Mutational spectrum

At the present time over 250 different disease-causing mutations, scattered throughout the gene, have been discovered[35,36]. These variants are distributed along the entire coding region of the gene and more than 50 per cent of them have been identified only once. The discovery that *BRCA1* was a large gene with many scattered mutations was discouraging, as its large size makes the possible number of mutations enormous and the technical aspects of finding them daunting; consequently, mutation screening would generally be time consuming and expensive. However, surveys of large numbers of linked families and high-risk women have revealed a few mutations that are seen recurrently[19,36]. These include a mutation within the ring-finger domain (185delAG) that is found in 12 per cent of *BRCA1* mutation carriers, a mutation within exon 20 (538insC) (10 per cent of mutations) and a mutation within exon 11 (4184del4). First searching for these mutations, therefore, most efficiently performs screening of high-risk women for *BRCA1* alterations. However, screening for many of the other 250 or more mutations will sometimes require scanning of the entire gene, a time-consuming and expensive task. Also, failure to detect a *BRCA1* alteration may be because the alteration is in a non-coding portion of the gene (such as an RNA regulatory region) that was not examined. So on the basis of mutation screening alone, patients cannot unequivocally be told that they do not harbour a *BRCA1* alteration. In the case of high-risk women there is also the chance that they have a germline alteration in another breast–ovarian cancer susceptibility gene[4].

BRCA2

Molecular epidemiology

BRCA2, the second breast cancer susceptibility gene, was mapped to chromosome 13q12-q13 by Wooster *et al.*[37] in 1994. About 1 year later, the same group reported a partial sequence of the gene structure (68 per cent) and identified six mutations[38]. In 1996 the Myriad Research Group reported the complete gene sequence and exonic structure of *BRCA2* and uncovered nine separate mutations[39]. Women with *BRCA2* mutations appear to have a breast cancer risk similar to that of women with *BRCA1* mutations (about 70 per cent by age 70 years)[40,41]. Ovarian cancer risk appears to be increased to a lesser degree than in *BRCA1* mutations; cumulative risk is estimated to be less than 10 per cent by age 70 years[41]. As noted previously, these ranges should be compared with the general population lifetime risk for breast and ovarian cancer of 11–12 per cent and 1·3 per cent respectively[26]. *BRCA2* germline mutations also result in increased susceptibility to breast cancer in men, where their lifetime risk is 5–7 per cent, some 200-fold greater than that of men in the general population[26]. It should be noted that these estimates for cancer associated with *BRCA1* and *BRCA2* mutations must be interpreted with caution, since they are derived from families studied for research purposes, who are characterized by early onset of cancer, multiple tumours, or both, and have met stringent criteria for autosomal dominant inheritance of cancer predisposition. Thus, they are likely to represent a sample biased toward increased risk and may overestimate the cancer risk associated with *BRCA1* and *BRCA2* mutations[42].

Structure and function

BRCA2 is almost twice as large as *BRCA1* and so even more complex to screen fully for mutations. It encodes a protein of 3418 amino acids. *BRCA2* is composed of 27 exons distributed over roughly 70 kb of genomic DNA. There is evidence that *BRCA2*, together with *BRCA1* and hereditary non-polyposis colonic cancer (HNPCC)-related genes, functions as a 'genomic caretaker', acting as the guardian of genome integrity by playing important roles in DNA repair[43,44]. Its mutation promotes neoplasia indirectly through increased genomic instability[44].

Mutational spectrum

Over 100 mutations have been described in *BRCA2*[8,37,45–49] that, like *BRCA1*, are not confined to a particular region of the gene. Like *BRCA1*, somatic mutations are very infrequently found in sporadic breast cancer[47,48,50]. There is increasing evidence that *BRCA1* and *BRCA2* are classic tumour suppressor genes (and not oncogenes). First, mutations that render *BRCA1* and *BRCA2* non-functional or absent are associated with tumour development, whereas oncogenes are modified in cancer cells in a way that increases, or deregulates, their normal function. In *BRCA1*- and *BRCA2*-linked families, tumour formation is frequently accompanied by loss of the chromosomal region harbouring the wild-type allele[40]. Approximately half of breast and ovarian tumours from mutation carriers show loss of the normal copy of *BRCA1* or *BRCA2*, which leaves behind only the copy of the gene that contains the inherited mutation[51,52]. Second, *BRCA1* mRNA levels are higher in normal breast epithelium than in sporadic breast tumours. Moreover, forced expression of a full-length *BRCA1* transgene has been associated with a growth inhibitory effect[53].

Pathology of *BRCA1*- and *BRCA2*-associated breast cancers

In *BRCA1*/*BRCA2*-associated breast cancer cases there are more medullary cancers than in control cases (13 *versus* 2 per cent). Similarly, among affected *BRCA1* and *BRCA2* mutation carriers there are more high-grade cancers than in control cases (grade 3, 66 *versus* 41 *versus* 36 per cent respectively)[54]. The presence of ductal carcinoma *in situ* in association with invasive cancer is less common in *BRCA1* cases than in controls, but is still considerable at 41 per cent. Other studies also suggest that *BRCA1*/*BRCA2*-associated tumours of the breast and ovary are frequently of high grade, aneuploid with a high S-phase fraction, with higher mitotic rates, less tubule formation, and are often oestrogen receptor, progestogen receptor and c-*erbB2* negative[55–58]. This suggests that *BRCA1*/*BRCA2*-associated breast cancers are highly proliferative tumours, but the biological defects responsible for this observation have yet to be elucidated.

These observations raised concern that breast cancer in mutation carriers is biologically more aggressive, resulting in higher mortality rates. Surprisingly, Lee *et al.*[59] recently found no difference in breast or ovarian cancer survival by mutation status, despite the presence of adverse prognostic factors among carriers. This study adds weight to the evidence indicating a generally similar cancer course in mutation carriers *versus* non-carriers. However, screening bias, potentially resulting from greater vigilance and earlier detection in identified carrier families, could be responsible for an appearance of improved survival among carriers[60]. The possibility of improved survival rate associated with *BRCA1*-associated tumours[57] compared with sporadic tumours of similar grade remains to be proven. As in other areas of rapidly evolving genetic knowledge, the final answer must await larger studies, with unbiased selection of cases and controls and objective measures of all relevant outcomes.

BRCA1, *BRCA2* and the risk of other cancers

As stated above, a major epidemiological characteristic among *BRCA1* and *BRCA2* mutation carriers is its strong association with ovarian cancer. Moreover, studies on other cancers in mutation carriers indicate that *BRCA1* and *BRCA2* mutations carry an increased risk of prostate and colonic cancer[4]. The risk of prostate cancer is estimated to be threefold higher in male mutation carriers than in the general population, with a cumulative risk of 8 per cent by the age of 70 years[24]. The risk of colonic cancer is estimated to be fourfold higher in both male and female mutation carriers, with a cumulative risk of 6 per cent by age 70 years[24]. The onset of these cancers does not appear to occur earlier than in sporadic cases. These molecular epidemiological data may have obvious practical implications.

Other genes involved in familial and sporadic breast cancer

p53 *gene*

The human *p53* gene is located on the short arm of chromosome 17. The p53 protein has an important biological function as a cell cycle checkpoint and controller of the intact genome, and it has the ability to respond to DNA damage by arresting the cell cycle and inducing DNA repair or apoptosis (programmed cell death). In the absence of functional p53, the cell escapes apoptosis and is able to survive and replicate the damaged DNA, resulting in genetic instability and predisposition to further DNA damage, such as gene amplification[6–8].

p53 is known to be a tumour suppressor gene that can be inactivated by point mutations[6]. The *p53* gene is mutated in about 50 per cent of all human cancer cases[61]. Most frequent are missense mutations resulting in single amino acid substitutions in the central hydrophobic domain involved in DNA binding[62]. The mutational spectra of the *p53* gene are tissue specific[63]. The mutational spectrum in breast cancer has some similarity to that of lung cancer[17]. This observation certainly requires further experimental verification, but seems to implicate chemical carcinogens in the aetiology of a subset of breast cancers. Breast tissue of smokers may be exposed to a biologically effective dose of carcinogens[64].

p53 was found to be associated with the Li–Fraumeni syndrome (LFS), an autosomal dominant cancer syndrome. Families with LFS have a high risk of soft tissue childhood sarcomas, breast cancer, and a diversity of additional malignant diseases, including brain tumours, leukaemia and adrenocortical carcinoma[65]. The onset of breast cancer is often at a very early age (20–30 years). Germline mutations in the *p53* gene have been identified in over 50 per cent of LFS families and in a number of families with some but not all of the features of the classical syndrome[65,66]. The absolute risk of breast cancer in mutation carriers has not been estimated precisely, but seems to be at least 50 per cent by age 50 years, with little increase in risk after the menopause[67], and so *p53* seems to be a major contributor of the occurrence of inherited breast cancer in the specific setting of LFS[68]. Available evidence suggests that germline *p53* mutations account for a very small proportion of breast cancer outside the LFS (or Li–Fraumeni-like syndrome). In population-based studies of breast cancer, *p53* germline mutations are found in less than 1 per cent of cases even at young ages[69,70]. By contrast, however, as previously noted, somatic mutations of *p53* are considered to be very common in breast cancer and other forms of malignancy, and may involve up to 50 per cent of sporadic cases of breast cancer[71].

PTEN *gene*

Cowden disease is a rare autosomal dominant syndrome in which affected members tend to develop bilateral breast cancer, multiple facial trichilemmomas, acral keratoses, oral papillomatosis, gastrointestinal polyposis, female genital tract tumours, and benign and malignant thyroid tumours[72]. The Cowden disease locus was mapped to chromosome 10q22-23[73–75]. This gene encodes for a novel phosphatase. Mutations are found in primary gliomas and carcinomas of the breast and kidney, as well as in related cancer cells. Subsequently, mutations in *PTEN* have been identified in multiple Cowden disease kindred[76], identifying *PTEN* as the gene responsible for Cowden disease when mutated.

The risk of breast cancer in women with Cowden disease is 30–50 per cent by age 50 years[77]. It is often bilateral and typically is diagnosed at a younger than average age[68]. Breast cancer has been diagnosed in patients with Cowden disease as young as 15 years of age[78]. The recognition that many site-specific breast cancer families do not have mutations in the breast cancer susceptibility genes *BRCA1* and *BRCA2* has led several groups to examine such families for germline alterations in *PTEN*. Thus far no such mutations have been identified[76,79,80]. These data provide strong evidence that *PTEN* does not account for hereditary breast cancer susceptibility outside families that are affected by Cowden disease. Finally, somatic *PTEN* mutations in primary breast cancer specimens have been identified only rarely[81].

Ataxia-telangiectasia gene

Ataxia-telangiectasia (AT) is a rare autosomal recessive disorder in which patients experience progressive neurological degeneration (e.g. ataxia, choreoathetosis and oculomotor abnormalities), telangiectases of skin and eyes, immunodeficiency, developmental abnormalities, a hypersensitivity to ionizing radiation, and an increased susceptibility to various cancers including breast cancer (approximately sevenfold relative risk) and haematological malignancies[82]. A series of families with site-specific breast cancer underwent study for evidence of linkage to the AT locus, but no evidence of linkage was found[83]. An observation suggesting potential importance for the AT gene as a risk factor for breast cancer is its high prevalence: an estimated 1 per cent of the general population may be AT heterozygous. Consequently, this gene could account for as much as 8 per cent of breast cancer in patients younger than 40 years and 2 per cent of all cases in patients between the ages of 40 and 60 years[84]. If this is true, the proportion of all breast cancer accounted for by the AT gene would be greater than that for *BRCA1* and *BRCA2* combined. So, although AT may not be an important contributor to the risk of familial breast cancer, it may be a major genetic risk factor for breast cancer in general[68]. It is worth noting that the significance of the high population frequency of AT heterozygosity may also be important in terms of the potential radiosensitivity of these carriers and the possibility of radiation-induced carcinogenesis. This may have critical implications for mammographic screening, but also for selecting the method of treatment in the surgical management of mutation carriers with breast cancer (i.e. breast-conserving surgery, which should be followed by radiotherapy, *versus* mastectomy)[78].

Other genes

Investigators have consistently noted that perhaps 10–20 per cent of families at high risk for breast cancer have no linkage to either *BRCA1* or *BRCA2*. This situation may imply the existence of additional, yet to be discovered, dominant susceptibility genes. A linkage analysis of eight families with linkage to neither *BRCA1* or *BRCA2* yielded preliminary evidence that a third gene (empirically called *BRCA3*) might be on chromosome 8p12-22[85]. None of these families had women with ovarian cancer. This 'syndrome', if it exists, is not yet well characterized. Another gene, encoded by sequences on chromosome 2, named *BARD1* (*BRCA1*-associated RING-domain 1) has recently been identified[86]. The role of *BARD1* in the development of both sporadic and familial breast and ovarian cancers is currently under investigation. Many other cancer-related genes, such as *myc*, c-*erbB2*, cyclin D1, *Mdgi* and *Tsg101*, have been shown to be involved in the tumorigenesis of breast cancers, although they do not give rise to familial breast cancer syndromes. It is likely that some of these genes might play a modifying role in familial breast cancer and, with time, they will become more prominent in the studies of the disease. Of note is the fact that, although some investigators reported a relative risk of breast cancer of about 5 among HNPCC mutation carriers, including *hMSH2*, *hMLH1*, *hPMS1* and *hPMS2* genes[87], overall reports suggest that the absolute risk is low in carriers of mutation of these genes[39].

Clinical implications

Risk estimation

Methods to detect reliably the earliest stages of breast cancer have been widely sought because the success of breast cancer treatment is influenced by how early a malignancy is diagnosed. Current methods for early detection rely on either physical examination to palpate a tumour or mammography[3]. The development of genetic tests that enable accurate risk assessment for individuals in high-risk families has been predicted to have substantial medical benefits. Significant and unprecedented media fanfare informed both medical professionals and the general public about exciting new discoveries in breast cancer genetics, namely the identification of two critically important breast cancer genes, *BRCA1* and *BRCA2*, helping to create an immediate demand for clinical tests for these genes. It is anticipated that the demand for DNA testing for *BRCA* mutations among individuals with a family history of breast cancer will expand even more rapidly in the near future[88].

With the discovery and cloning of *BRCA1* and *BRCA2*, both enthusiasm and concern have been expressed about genetic testing. Because identification of *BRCA1* and *BRCA2* is so recent, knowledge about how to translate this powerful genetic information into clinical practice without harming the patient is limited[20,42,89,90]. It seems clear that before such testing is offered healthcare providers, laboratory professionals and individuals seeking testing should have a clear understanding about the basic concepts, strategies and limitations of this relatively new application of genetic testing for presymptomatic detection of mutations. Any physician who offers genetic testing should be aware, and able to communicate, the benefits and limits of current testing procedures, and the range of prevention options available to patients and their families. Moreover, he or she must assure that informed consent has been given by the patient as an integral part of the process of genetic predisposition testing, whether such testing is offered on a clinical or research basis (*Table 1*).

Despite the rapid pace of research in cancer genetics, none of the cancer susceptibility tests currently available is appropriate for screening of asymptomatic individuals in the general population. In the setting of well-defined cancer susceptibility syndromes, however, the identification of a mutation in an affected member of the family can be utilized

Table 1 Basic elements of informed consent for germline DNA testing

1. Information on the specific test being performed
2. Implications of a positive and negative result
3 Possibility that the test will not be informative
4 Options for risk estimation without genetic testing
5. Risk of passing a mutation to children
6. Technical accuracy of the test
7 Risks of psychological distress
8. Risks of insurance or employer discrimination
9. Confidentiality issues
10 Options and limitations of medical surveillance and screening following testing

Modified from American Society of Clinical Oncology[91]; reproduced with permission from Lippincott, Williams and Williams as a critical baseline in the testing of other family members. According to the American Society of Clinical Oncology, current criteria defining families with the highest likelihood of harbouring *BRCA1* and *BRCA2* mutations in hereditary breast–ovarian syndrome are: (1) family with more than two breast cancer cases and one or more cases of ovarian cancer diagnosed at any age, (2) family with more than three breast cancer cases diagnosed before 50 years, and (3) sister pairs with two of the following cancers diagnosed before age 50 years – two breast cancers, two ovarian cancers, or a breast and ovarian cancer[91]. A negative test in the setting of a known mutation in a family may provide significant emotional relief as well as allow a decreased frequency of medical surveillance.

Despite these benefits, genetic testing also poses several risks. In families where a mutation has been identified, a positive genetic test result can create anxiety, 'parental guilt', 'survivor guilt' and even depression; it may lead to preventive or screening interventions of presumed, but unproven, efficacy. Uncertainties surrounding the prognosis and best management for identified individuals still remain, especially for the small proportion of women with no family history of breast or ovarian cancer who are found to carry germline *BRCA1* or *BRCA2* mutations[20], since the role of these genes in sporadic cases of breast cancer has not yet been clearly defined. A false-negative test result may result in undue reassurance for an individual at markedly increased risk by virtue of family history, but with a negative test result for a particular gene. This may be due to the fact that tests for a known mutation are very sensitive and specific. However, when no mutation has been identified, a negative *BRCA1* or *BRCA2* mutation result is not very informative, because there is currently no test that is sensitive for any and all possible mutations[26]. There is therefore a need for ongoing research, rigorous quality assurance of genetic testing, and continued medical education about the interpretation of genetic susceptibility tests.

Clinical implications for unaffected mutation carriers

As previously noted, unaffected mutation carriers have a particularly increased lifetime risk of developing breast and/or ovarian cancer. These women may choose either increased medical surveillance to detect and treat early tumours or bilateral prophylactic surgery (mastectomy and/or oophorectomy) in an attempt to eradicate the tissues that have the greatest potential of becoming malignant.

In principle, the preferred management option for gene mutation carriers would be to offer targeted screening for tumours to which the tumour predisposes. Recommendations for breast cancer surveillance apply to female carriers of *BRCA1/BRCA2* mutations (*Table 2*). Unfortunately, the effects of screening are unproven and no data are available, at present, regarding a programme of optimal surveillance.

Breast cancer surveillance

Breast self-examination and clinical examination. Monthly self-examination is recommended beginning early in adult life

Table 2 Breast, ovarian, prostate and colonic cancer surveillance for *BRCA1* and *BRCA2* mutation carriers*

	Recommendation	Benefit
Breast cancer		
Self-examination	Monthly, beginning at age 20 years	Unproven
Clinical examination	Annually or twice yearly, beginning at age 25–35 years	Unproven
Mammography	Annually, beginning at age 25–35 years	Risks and benefits not established
Breast ultrasonography	Annually, beginning at age 25 years	Unproven
Ovarian cancer†		
Transvaginal ultrasonography with colour Doppler	Annually or twice yearly, beginning at age 25–35 years	Unproven
Serum CA-125 level	Annually or twice yearly, beginning at age 25–35 years	Unproven
Prostate cancer		
Digital examination	Annually	Unproven
Serum prostate-specific antigen level	Annually	Unproven
Colonic cancer		
Faecal occult blood testing	Annually, beginning at age 50 years	Relevance of population-based data uncertain
Flexible sigmoidoscopy	Every 3–5 years, beginning at age 50 years	Relevance of population-based data uncertain

*Recommendations and practice for screening and monitoring mutation carriers may differ between countries †Ovarian cancer risk is lower in *BRCA2* mutation carriers Modified from Burke *et al.*[42], reproduced with permission from the American Medical Association (by the age of 20 years) to establish a regular habit and allow familiarity with the normal characteristics of breast tissue. Annual or twice yearly clinical examination is recommended, beginning at age 25–35 years. Although in previous studies it has been shown that breast self-examination and clinical examination fail to reduce the mortality rate from breast cancer[92,93], it is possible that the limited sensitivity of mammography in younger women makes breast self-examination and clinical examination of greater value for *BRCA1*/*BRCA2* mutation carriers than for women of average risk[42].

Mammography. Annual mammography is suggested, beginning at age 25–35 years. Within this interval, the age at which regular screening is initiated should be determined by the preferences of the individual being screened, taking into account the relatively limited sensitivity of mammography in younger women and the potentially increased risk of breast cancer from repeated radiation exposure when mammography is started at an early age. This risk may be even higher in individuals with an inherited cancer predisposition. For example, carriers of the AT gene and the *p53* gene are known to have increased radiosensitivity. No data are available on radiation risk or sensitivity of early mammography in *BRCA1*/*BRCA2* mutation carriers[42]. Ideally, annual mammography in young mutation carriers should be performed as part of research studies in an effort to establish clear guidelines and to determine the optimal management of these women.

Breast ultrasonography. Because of these concerns about the use of mammography at an early age in mutation carriers, annual breast ultrasonography has been proposed as an alternative for the screening of these high-risk young women[94]. However, the role of this test as a screening tool in this setting remains undefined.

Breast magnetic resonance imaging. Although magnetic resonance imaging has been proposed for the screening of mutation carriers[94], experience remains extremely limited, precluding any recommendation.

Ovarian, prostate and colonic cancer surveillance

Ovarian cancer surveillance. For *BRCA1* mutation carriers, ovarian cancer surveillance should be considered. Estimation of serum CA-125 levels (annually or twice yearly), beginning at age 25–35 years, is recommended[42,78,95–98]. A raised serum CA-125 concentration occurs in the majority of asymptomatic ovarian cancers[95,96]. However, CA-125 estimation lacks sensitivity and specificity; fewer than 50 per cent of early stage tumours are associated with increased serum levels, while raised levels have been observed in a variety of non-malignant conditions, as well as in non-gynaecological malignancies[95].

Transabdominal and transvaginal ultrasonography have been studied as non-invasive screening tools, and the latter is currently the preferred modality because it improves discrimination between benign and malignant pathology[96,97]. Among *BRCA1* mutation carriers, screening transvaginal ultrasonography should be performed annually or twice yearly, beginning at age 25–35 years[42]. Ovarian cancer surveillance is also an option for *BRCA2* mutation carriers, but their lower risk reduces the likelihood of benefit[98].

Prostate cancer screening. There are insufficient data to make a recommendation for or against prostate cancer screening for male mutation carriers. These men should be informed of their increased risk of prostate cancer and counselled that the absolute risk is much lower than the risk for breast or ovarian cancer in female carriers; annual digital rectal examination and measurement of serum prostate-specific antigen should be considered in these male carriers[42]. The American Cancer Society recommends prostate cancer screening at age 50 years[99]; however, an earlier screening for men in high-risk groups should be considered.

Colorectal cancer screening. Male and female mutation carriers should be informed of a potential increased risk of colorectal cancer and encouraged to follow screening recommendations for the general population[42,99].

Preventive strategies

Prophylactic surgery

The role of prophylactic surgery remains controversial, and both families and physicians raise questions about the effectiveness of this aggressive approach in mutation carriers. In the 1970s and 1980s prophylactic mastectomy became a popular option for high-risk women; however, over the past decade, with the advent of sophisticated mammographic screening techniques, its use has waned. Prophylactic mastectomy might also seem a rather drastic option in this current era of early breast cancer management by means of breast conservation therapy. However, for some women with extreme anxiety it may be a valid option[78]. Prophylactic mastectomy in *BRCA1*/*BRCA2* carriers results in a gain in life expectancy (ranging from 2·9 to 5·3 years)[100,101]. This gain in life expectancy is substantially greater the younger the age at which the mastectomy is performed[101].

Most experts prefer simple mastectomy for prophylactic procedures, with or without reconstruction[102]. However, it is important to appreciate that prophylactic mastectomy has a significant failure rate, with subsequent cancer being documented in many case reports in observational studies[103–105]. Indeed, in high-risk patients, the development of cancer following mastectomy has ranged from 1 to 9 per cent[78,106]. The reason for this is that breast tissue occurs in the chest wall, axilla and abdomen, and so it is virtually impossible to remove all such tissue surgically[102,105,107]. In particular, the nipple-sparing subcutaneous mastectomy via an inframammary incision is estimated to leave about 5–15 per cent of breast tissue[108]. Women undergoing prophylactic mastectomy should be informed that, while their risk of breast cancer may be reduced, it will not be eradicated completely.

There is insufficient evidence for or against prophylactic oophorectomy as a measure for reducing ovarian cancer risk among mutation carriers. Women with *BRCA1* mutations should be counselled that this is an option available to them. The uncertainty of current methods for detecting early ovarian cancer, and the high mortality rate associated with this cancer, have been cited as reasons to consider prophylactic oophorectomy[98]. Those considering this operation should be counselled that primary peritoneal carcinoma, histopathologically indistinguishable from ovarian carcinoma, can occur after the procedure[109]. The incidence of peritoneal carcinoma is between 2 and 10 per cent, occurring 1–27 years after the prophylactic oophorectomy[109,110]. These findings imply that, despite oophorectomy, ovarian peritoneal cell rests may be left behind and can undergo malignant transformation.

Observational data have failed to demonstrate statistically significant evidence for risk reduction. Indeed, hypothetical modelling, analysing the gains in life expectancy from prophylactic oophorectomy, have shown much smaller increments (ranging from 0·3 to 1·7 years), compared with that of prophylactic mastectomy[101]. The optimum age for the procedure has not been established, but the mean age for ovarian cancer in hereditary breast–ovarian families is in the mid 40s.

A recent National Institutes of Health consensus conference recommended that women with two or more first-degree relatives with ovarian cancer be offered prophylactic oophorectomy after completion of childbearing or at age 35 years, based on mean age of ovarian cancer occurring in the mid to late 40s[98]. Balanced against the potential but unproven protective effect of oophorectomy are the risks and symptoms of surgical menopause[111]. These include increased vasomotor and other menopausal symptoms, and increased risk of osteoporosis and cardiovascular disease. Treatment with hormone replacement therapy to decrease this risk may increase the risk of breast cancer. Oophorectomy is also an option for *BRCA2* mutation carriers, but their own lower risk reduces the likelihood of benefit[42].

In conclusion, neither prophylactic mastectomy nor prophylactic oophorectomy provides complete protection against the subsequent development of malignant disease and so ongoing surveillance is still required. Obviously, women should be extensively counselled about the matters before any prophylactic surgery.

Chemoprevention

The option of chemoprevention of breast cancer in gene carriers has been proposed as an alternative to prophylactic surgery. Potential primary prevention medications, such as tamoxifen[112] and raloxifene[113], reduce breast cancer risk. For women who have already had one primary breast cancer, the risk of a second primary tumour in the contralateral breast is reduced by as much as 40 per cent by adjuvant tamoxifen[114]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial recruited more than 13 000 women at increased risk of developing breast cancer (because they were aged over 60 years, or were 35–59 years of age with a 5-year predicted risk for breast cancer of at least 1·7 per cent, or had a history of lobular carcinoma *in situ*)[115]. In this study tamoxifen reduced the incidence of breast cancer by 49 per cent[116]. However, a number of issues still need to be resolved. Is the cancer only delayed by tamoxifen? What effect does this have on eventual mortality rates? If there is an enduring benefit, which subsets of women should be targeted for maximal effect? Moreover, the specific effects on breast cancer risk in *BRCA1*/*BRCA2*-positive women are as yet unknown, as are the costs and side-effects of therapy. The most serious side-effect of tamoxifen has been its reported increased risk of endometrial carcinoma[117] and so caution is needed in the Lynch-type families (HNPCC) where there may already be a fourfold increased risk of endometrial carcinoma development.

It has been shown recently that raloxifene reduces the risk of invasive breast cancer by 76 per cent in postmenopausal women during 3 years of treatment and this protective effect is not associated with an increased risk of endometrial cancer[118]. Tamoxifen usage in younger women may be limited because of its potential teratogenic effects. As with other medications, evidence of an acceptable risk : benefit ratio is needed before these therapies can be recommended[42].

Environmental and lifestyle factors

Hormone replacement therapy. While the short-term use of hormone replacement therapy (HRT) in the management of menopausal symptoms is considered quite safe, the role of long-term HRT in breast carcinogenesis remains controversial[119]. There are insufficient data to make a recommendation concerning use or avoidance of HRT by *BRCA1* and *BRCA2* mutation carriers.

Oral contraceptive use. In the general population, oral contraceptive use is associated with a slight increase in breast cancer risk; however, this is only a short-term effect and the greatest risk occurs in young women using the contraceptive pill long term before a first full-term pregnancy[120]. On the other hand, several studies have shown a reduced relative risk of ovarian cancer in users of oral contraceptives, including those with a family history of ovarian cancer[121]. No data are currently available on the effect of oral contraceptives on ovarian cancer risk in *BRCA1*/*BRCA2* mutation carriers.

Other factors. Numerous studies have identified potentially modifiable non-genetic risk factors for breast and ovarian cancer, including reproductive factors, high levels of dietary fat, high alcohol consumption, low antioxidant vitamin intake, excessive radiation exposure and decreased physical activity[122]. No data are available on the effect of lifestyle modification in *BRCA1*/*BRCA2* mutation carriers.

Clinical implications for affected mutation carriers

As stated above, breast cancers in known *BRCA1*/*BRCA2* mutation carriers are frequently associated with adverse prognostic factors, implying a more aggressive biological behaviour. Some authors report that hereditary breast cancer is more often multicentric, probably because the entire breast parenchyma is at a higher risk as a consequence of the genetic predisposition of breast cells[123]. Moreover, radiation risks may be higher in this group of patients. For all these reasons, the appropriateness of breast conservation therapy in known mutation carriers is being evaluated, and treatment by mastectomy rather than breast conservation may need to be undertaken more frequently, or at least the criteria for undertaking breast conservation therapy may need to be applied more stringently, and this procedure performed mostly under clearly favourable circumstances[35,78]. Of course, if breast conservation therapy is chosen, close and long-term surveillance of both breasts is mandatory. This is especially important since *BRCA1*/*BRCA2* mutation carriers with breast cancer are at an increased risk of developing a second breast cancer or bilateral disease; indeed the cumulative risk of developing a second breast cancer is estimated to be 60–80 per cent for affected mutation carriers who live to the age of 70 years[23,24,39]. Some women may opt for a prophylactic mastectomy on the unaffected site.

Future perspectives

Today, knowledge of the molecular basis of breast cancer and genetic testing for cancer susceptibility is inadequate[124]. Besides the genes described in this review, others might play crucial roles in breast carcinogenesis. Modifying genes and environmental factors may influence the ultimate phenotypic expression of a mutated gene. Despite these significant defects in our knowledge, people tend to overemphasize the benefits of testing and to downplay its risks and limitations[125]. It is anticipated that the demand for testing among individuals with a family history of breast cancer will expand rapidly[20]. A survey of female first-degree relatives of patients with breast cancer found that about 95 per cent of respondents desired presymptomatic genetic testing[88]. Many patients who have been studied and who were found to carry a *BRCA1* or *BRCA2* mutation indicated that they would increase their overall surveillance activities[26]. Many indicated that they would consider the option of prophylactic mastectomy or oophorectomy, or both. However, as research goes forward, puzzling questions need to be addressed about the effects of gene mutations and their clinical implications.

With respect to surveillance, the potential clinical implications of molecular biology in breast cancer management relate to the oncological expectation that early detection of cancer leads to the therapeutic benefit of a reduction in morbidity and mortality rates. In addition to this benefit, gene therapy offers a new, theoretically attractive, approach to breast cancer management. A variety of molecular processes can be introduced by gene transfer which, in principle at least, arrest tumour growth. This may be accomplished through alteration of the metabolic or signalling pathways within the breast cancer cell by targeting specific genetic alterations (such as c-*erbB2*, *p53*, c-*myc* and *BRCA1*) or through enhancement of the immune response to the tumour cells (passive and active immunization, introduction of cytokines and expression of T cell co-stimulatory molecules)[6,53,126]. However, several major obstacles have yet to be overcome for these approaches to be successful clinically[126].

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Management of the axilla in operable breast cancer treated by breast conservation: a randomized clinical trial

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Background: In the treatment of operable breast cancer by breast conservation, the extent of axillary dissection, the need for radiotherapy to the axilla and the morbidity associated with these procedures have not been assessed adequately.

Methods: Patients with operable breast cancer were randomized to have level III axillary node clearance (232 patients) or axillary node sample (234 patients). Radiotherapy to the axilla was given selectively. Radiotherapy was not given to those who had an axillary clearance. In the early part of the study all patients who had node sample were treated by radiotherapy (54 patients); subsequently this was modified to include only those who were node positive. The morbidity to the shoulder and arm was assessed before and after operation by measuring upper limb volume and circumference, and combined glenohumeral and scapular movement and muscle power.

Results: Comparing the two surgical policies, no difference was found in local (axillary clearance 14 *versus* sample 15), axillary (eight *versus* seven) or distant (29 *versus* 29) recurrence. There was no statistically significant difference in 5-year survival rate (clearance 82·1 *versus* sample 88·6 per cent). Morbidity was least in those who had a node sample and no radiotherapy to the axilla. Radiotherapy to the axilla in patients who had a node sample resulted in a significant reduction in range of movement of the shoulder, e.g. mean(s.e.) 2·2(0·6) cm reduction in lateral rotation at 3 years. Surgical axillary clearance was associated with significant lymphoedema of the upper limb, e.g. 4·1(0·7) per cent increase in arm volume at 3 years.

Conclusion: A selective policy for the management of the axilla is associated with no increase in axillary recurrence or mortality rate compared with routine axillary node clearance. Patients who are node negative after axillary sample can avoid radiotherapy or axillary clearance.

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Introduction

The role of surgery and radiotherapy in the treatment of the axilla in patients with breast cancer managed by breast conservation has not been evaluated adequately. Although clinical trials[1–3] have demonstrated the efficacy of breast conservation, the extent of surgery to the axilla and the need for radiotherapy have not been assessed in a prospective randomized trial. Neither has there been an adequate assessment of the morbidity associated with the surgical procedures and radiotherapy.

Routine surgical clearance of the axillary lymph nodes has been advocated[1,2,4], yet over 50 per cent of tumours up to 5 cm in diameter and 90 per cent of those below 1 cm will have no involvement of axillary nodes[5]. Unfortunately, there is no reliable preoperative method of determining axillary node involvement[6–10]. Histological examination of axillary nodes obtained by a four-node sampling procedure has been shown to stage the axilla accurately[11].

The aims of this study were to compare the efficacy of different surgical approaches (axillary node sample or node clearance) in patients with operable breast cancer being treated by breast conservation, and to assess the morbidity associated with these procedures and radiotherapy.

Patients and methods

Between 1987 and 1995, 466 patients aged under 70 years with unilateral invasive breast cancer of clinical size 4 cm or less and no evidence of metastatic disease were randomized in this trial. Patients were excluded if the tumour was clinically multicentric or considered locally inoperable (T_4), the axillary nodes were fixed (N_2) or the patient had a history of previous invasive carcinoma at any site (except skin basal cell carcinoma). Patients had to be considered suitable for either of the options in the study. The protocol was approved by the local ethics committee and informed consent was obtained from all patients.

Patients were randomized before operation to one of two treatment options, an axillary clearance or an axillary node sample. Options were determined by contacting the Scottish Cancer Trials Office who registered the patient and gave the next available treatment option from a list derived using randomized permuted blocks of eight.

Surgery

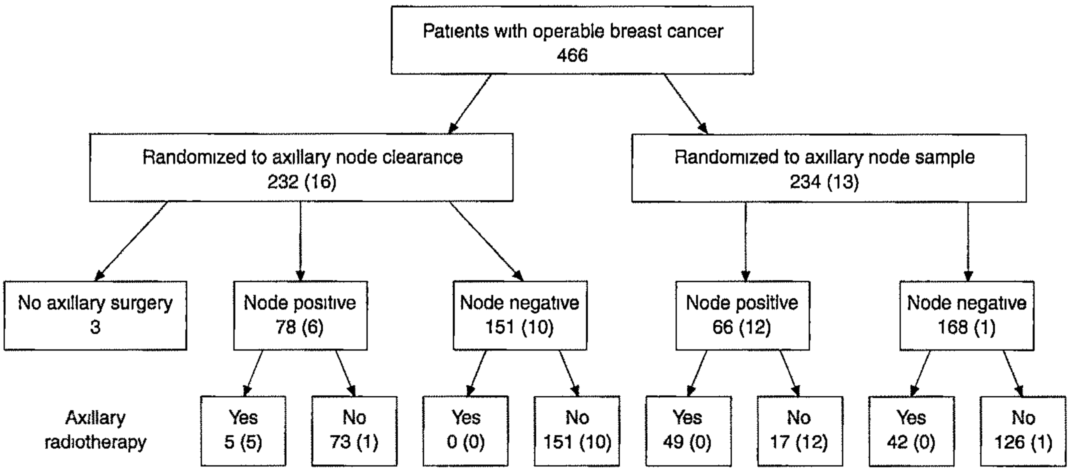
The aim of the axillary node sampling technique was to obtain at least four palpable lymph nodes from the axilla, starting at the axillary tail and working upwards. This was done through a transverse incision between the latissimus dorsi and pectoralis muscles. The axillary tail was mobilized off the chest wall and serratus anterior muscle. The nodes were identified by palpation. No other localization aids were used.

A level III axillary clearance was performed through a transverse axillary incision with division of the pectoralis minor muscle. The thoracodorsal trunk and long thoracic nerve were preserved. In the majority of patients the intercostobrachial nerve and the lower intercostobrachial nerves were divided.

Radiotherapy

Patients routinely received postoperative radiotherapy to the breast. However, 48 patients were randomized to the 'no radiotherapy' arm in the Scottish Conservation Trial[12], which ran concurrently, and therefore did not receive breast or lymphatic irradiation. Of these, five were node positive and the remainder node negative. Patients who underwent an axillary clearance did not receive radiotherapy to the axillary region (*Fig. 1*). After an axillary sample that revealed involved nodes, all patients received axillary radiotherapy, apart from the five referred to above.

The policy before 1991 was for all patients who had an axillary sample to receive routine regional lymphatic radiotherapy. Between 1987 and 1990, 39 patients who underwent axillary sample and whose axillas were node negative received axillary radiotherapy. Thereafter node-negative patients, apart from three with fewer than four nodes found on axillary sample, did not receive axillary radiotherapy. This policy change resulted from data



Randomization errors

	Axillary node clearance	Axillary node sample
Benign lesions	2	2
Non-invasive cancer	5	3
Stage IV disease	2	0
Bilateral disease	1	0
Previous cancer	1	0

Fig. 1 Randomization of 466 patients in the study and treatment received. Values in parentheses indicate patients in whom the protocol was violated

accumulated from other studies in the unit which compared axillary sampling with clearance. These showed that the two surgical procedures were of equal qualitative prognostic value[11] and that there was no benefit provided by irradiating a node-negative axilla[13].

The breast irradiation technique involved the use of a pair of tangential fields, 45 Gy target absorbed dose in 20 fractions over 4 weeks or 45 Gy in 25 fractions over 5 weeks for larger breasts, plus a boost to the tumour bed by interstitial implant (20 Gy to 85 per cent reference isodose using the Paris method of dosimetry) or electrons (15 Gy at the 100 per cent isodose in five daily fractions over 1 week). The regional lymphatics were treated by a direct anterior field covering the axilla and supraclavicular fossa with a posterior 'axillary' boost bringing the mid-axillary dose to 45 Gy given in 20 fractions over 4 weeks. From August 1990 the posterior axillary field was changed from 20 daily fractions to ten fractions on alternate days over 4 weeks.

Systemic adjuvant therapy

Patients received postoperative adjuvant hormone or chemotherapy depending on the results of pathology including axillary node histology and oestrogen receptor status. The same policy was followed for both randomized groups (*Table 1*).

Statistical analysis

Survival and other time-dependent variables subject to censoring are presented using Kaplan–Meier curves and were tested for statistically significant differences between the randomized treatment groups using the log rank test. The variables used to assess morbidity were analysed using an analysis of covariance, in which the corresponding preoperative measurement was used as a covariate. In this analysis, three groups of patients were compared: those who experienced node sampling alone; those who had axillary clearance; and those who received radiotherapy to the axilla after node sampling. Separate analyses were performed for each follow-up group. When overall differences between the three groups were statistically significant at the 5 per cent level, pairs of treatments were then compared. In the presentation of results, findings are shown in graphical form, and the results of significance testing are only shown when they clarify the interpretation of the results.

Assessment of morbidity

Arm volume, circumference and combined glenohumeral and scapular movement and muscle power were measured by one individual (C.T.). Both the treated and untreated arms were examined before operation, at 6 months and after 1, 2 and 3 years. Swelling of the arm was assessed by water displacement and measurement of the circumference of the arm 15 cm above and below the olecranon process.

Table 1 Clinical characteristics

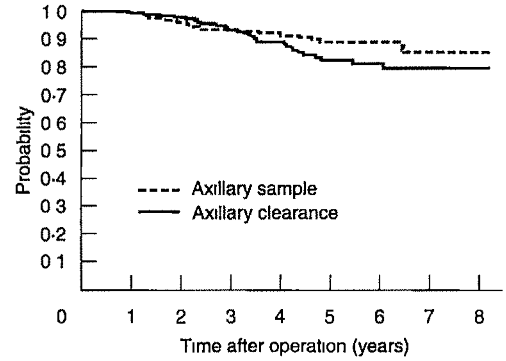
	Axillary clearance ($n=232$)	Axillary sample ($n=234$)
Median age (years)	54	54
Menopausal status		
Premenopausal	86	84
Perimenopausal	6	6
Postmenopausal	139	144
Not known	1	0
Clinical tumour size (cm)		
≤ 1	33	21
>1–≤ 2	57	68
>2–≤ 3	87	96
>3	55	48
Not assessable	0	1
Pathological tumour size (cm)		
≤ 1	35	24
>1–≤ 2	102	107
>2–≤ 3	44	60
>3	11	13
Not assessable	40	30
Tumour type		
No special type	177	176
Lobular	11	11
Tubular	16	13
Non-invasive	5	3
Other	23	31
No. of axillary nodes*	15 (4–36)	5 (2–12)
Pathological node status		
Node negative	151	168
Node positive	78	66
Not known	3	0
Adjuvant therapy		
Tamoxifen	163	174
Chemotherapy	26	28
Ovarian suppression	11	6
Chemotherapy + tamoxifen	10	9
None	22	17

*Values are median (range)

Shoulder joint mobility was assessed by measuring elevation through flexion, abduction, medial and lateral rotation[14]. Muscle power was assessed using a graduated spring to measure flexion, extension, abduction and adduction of the shoulder joint. The best of three recordings was taken in each case.

Results

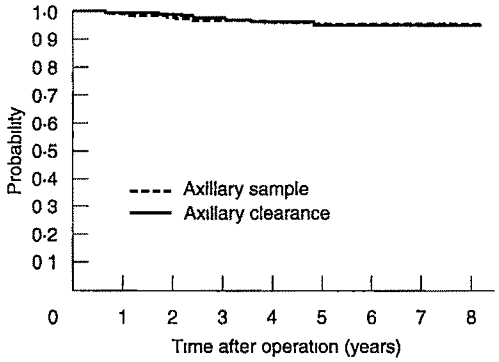
A total of 466 patients were randomized in the study. Initial diagnosis of breast cancer was based on clinical assessment,



No at risk

Axillary sample	234	221	193	164	125	85	61	29	5
Axillary clearance	232	219	198	164	125	82	57	34	2

Fig. 2 Time until death (all causes) according to axillary sample or clearance by intention to treat ($P = 0{\cdot}20$, log rank test)



No at risk

Axillary sample	234	224	198	169	130	87	63	29	5
Axillary clearance	232	221	200	170	130	86	59	34	2

Fig. 3 Time until regional recurrence (axilla) according to axillary sample or clearance by intention to treat ($P = 0{\cdot}94$, log rank test)

mammography and cytology. Four patients were subsequently found to have benign disease while a further eight had non-invasive cancer. After randomization, 29 patients did not receive their allocated option, the majority either because of refusal by the patient to undergo the randomized option or because further surgery was carried out, i.e. an axillary clearance after an initial sample (*Fig. 1*).

All patients have been included and analysed on an intention-to-treat basis in their randomized groups when assessing recurrence and survival. For analysis of morbidity, patients were analysed by actual treatment received.

Table 1 shows pretreatment characteristics of patients, the postoperative data on pathological size and pathological node status in the two randomized groups, and the adjuvant systemic therapy received by patients, the majority of whom were prescribed tamoxifen.

Survival

Median follow-up was 4·1 years. There was no significant difference in overall survival between the two groups (*Fig. 2*) ($P = 0{\cdot}20$, log rank test) or in disease-free survival ($P = 0{\cdot}68$). The estimated 5-year survival rate (standard error) was 88·6(2·5) per cent in the axillary sample group and 82·1(3·1) per cent in the clearance group. The corresponding disease-free survival rates were 79·1(3·1) and 76·0(3·5) per cent respectively. Nine patients died without evidence of breast cancer relapse, three in the axillary clearance group and six in the axillary sample group. Three patients died from a myocardial infarct, three from a second cancer (ovary, lung, uterine sarcoma), one after a road traffic accident, one from septicaemia after non-cancer bowel surgery and there was one suicide. One other patient developed distant metastases that may have originated from the breast cancer or subsequent colonic cancer. The other 44 deaths were all due to breast cancer.

Table 2 Locoregional and distant relapse from breast cancer

Site of relapse	Axillary clearance ($n=232$)	Axillary sample ($n=234$)
Local		
Breast	14	15
Regional		
Axilla	8	7
Supraclavicular fossa	4	2
Axilla + supraclavicular fossa	0	1
Distant	29	29

Recurrence

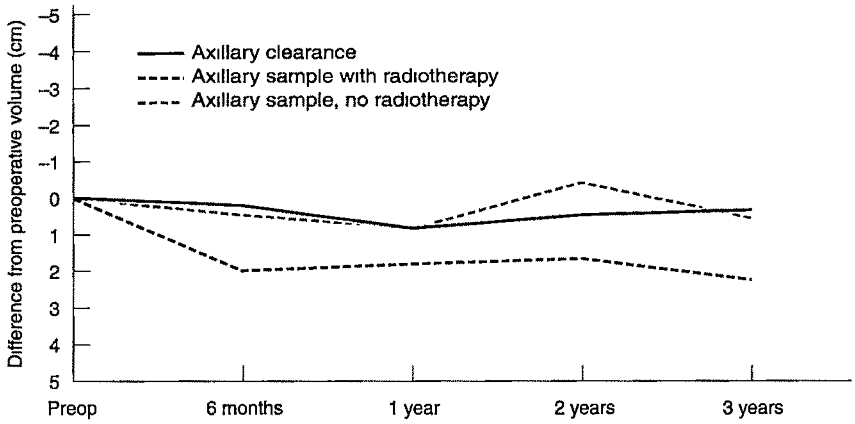
There was no difference in time to axillary recurrence in the two groups (*Fig. 3*) ($P = 0{\cdot}94$) or in time to breast recurrence ($P = 0{\cdot}97$). The number and sites of relapse up to the time of analysis are shown in *Table 2*.

Morbidity

Some 324 patients completed the multiple morbidity assessments and were analysed by treatment received (sample without radiotherapy to axilla 87, sample with radiotherapy to axilla 74, axillary clearance 163).

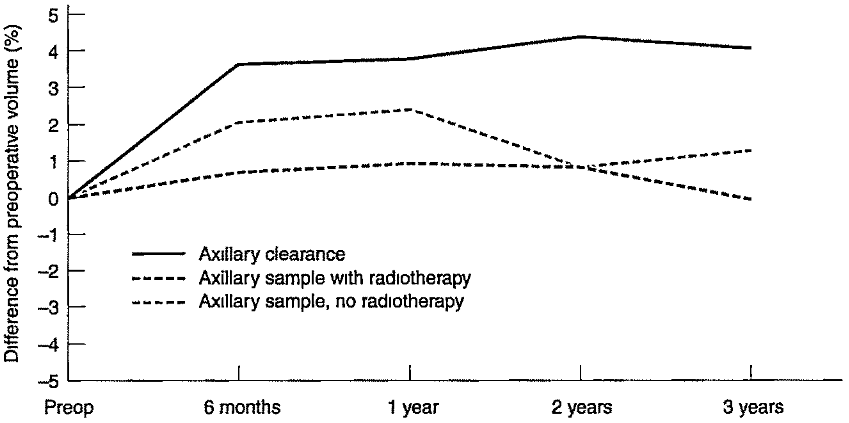
Range of shoulder movement

At 6 months, patients who had an axillary clearance and those who had a node sample and radiotherapy had a



Mean(s e.) difference (cm) (*n*)	6 months	1 year	2 years	3 years
Axillary clearance	0·13(0·39) (132)	0·77(0·40) (128)	0·38(0·43) (117)	0·24(0·43) (110)
Axillary sample with radiotherapy	1·91(0·56) (64)	1·75(0·56) (66)	1·57(0·60) (60)	2·19(0·59) (59)
Axillary sample, no radiotherapy	0·34(0·59) (59)	0·72(0·62) (55)	–0·48(0·65) (52)	0·43(0·64) (50)

Fig. 4 Comparison of lateral rotation of the shoulder in the three treatment groups



Mean(s e) percentage of preoperative arm volume (*n*)	6 months	1 year	2 years	3 years
Axillary clearance	103·57(0·519) (126)	103·74(0·57) (119)	104·37(0·73) (108)	104·07(0·73) (103)
Axillary sample with radiotherapy	100·69(0·779) (56)	100·95(0·81) (59)	100·84(1·03) (54)	100·01 (1·03) (52)
Axillary sample, no radiotherapy	102·04(0·766) (58)	102·47(0·85) (54)	100·81(1·06) (51)	101·28(1·07) (48)

Fig. 5 Comparison of arm volume in the three treatment groups, adjusted for the untreated arm

significantly reduced range of flexion compared with those who underwent node sample without radiotherapy ($P = 0{\cdot}003$ and $P = 0{\cdot}004$ respectively). However, the axillary clearance group improved with time, and by 3 years was not significantly different from the node sample alone group ($P = 0{\cdot}1$). Abduction was not affected by a node sample or radiotherapy but was slightly reduced after axillary node clearance.

Lateral rotation was reduced in the radiotherapy group at 6 months and deteriorated with time, as did medial rotation (*Fig. 4*). Lateral rotation was not affected by clearance or node sample alone. The axillary clearance group had a reduction in medial rotation at 6 months but this improved with time.

Shoulder muscle power

There were no differences between the groups in the power to flex the shoulder at any time point. Interestingly, there was an increase in power compared with preoperative measurements. At 6 months patients who had radiotherapy had a reduction in shoulder extension. With time all groups improved to above preoperative measurements. No difference in abduction was found when groups were compared with each other or with preoperative measurements. At 6 months and 1 year the radiotherapy and clearance groups had a reduction in the power to adduct, but by 3 years this improved to better than the preoperative measurement.

Arm swelling

After axillary clearance there was an early mean increase in arm volume of 4 per cent that remained constant over the next 2·5 years. After sample there was also an increased volume, but at 2 per cent this was less than that after axillary clearance and it improved with time (*Fig. 5*).

Measurement of the girth of the upper arm showed little difference in the three groups. The girth of the forearm increased after axillary clearance and progressed with time. However the main increase was during the initial 6 months. At 3 years the forearm girth was significantly greater after axillary clearance than after node sample alone ($P = 0{\cdot}005$) or node sample and radiotherapy ($P = 0{\cdot}04$).

Discussion

Locoregional control of breast cancer is important not only because of the psychological effects of local relapse but also because of the association with improved survival[15,16]. Management of the breast by wide excision of the tumour and radiotherapy is well established, while treatment of the axilla is more controversial. This study demonstrated that a selective policy of treatment of the axilla produces survival rates and locoregional control similar to those of an unselected radical surgical approach. The ideal would be to have an acceptable, non-invasive method of determining the status of the axilla before surgery; no interference to the axilla would be necessary in those shown to be node negative. Until this is available, histological assessment of the axillary nodes is still required both for staging and decisions about treatment. The number of nodes involved gives further prognostic information that might influence the type of adjuvant therapy, and is presently under study in some centres.

It has previously been demonstrated in this unit[11] that the four-node sample technique is an accurate way of staging the axilla, although others have reported difficulties[17,18]. Sentinel node biopsy, in which the first node to drain the tumour-bearing area is identified and excised, may prove an alternative technique[19]. However, several aspects of this method still require to be resolved[20,21].

Examination of the nodes by frozen section allows the decision to proceed to an immediate axillary clearance in those who are node positive. However, frozen section of the lymph nodes is technically difficult, false negatives occur[22] and it is time consuming. Newer methods such as immunohistochemistry are being developed for peroperative assessment.

An alternative treatment to axillary clearance for the sampled axilla found to be node positive is radical radiotherapy. This produces similar results to axillary clearance[23,24]. In deciding how to treat the axilla, the morbidity of the various procedures has to be considered. Previous studies have not been randomized, have not considered the changes with time and have used arbitrary decisions as to what constitutes significant morbidity[14,25–27]. Subjective evaluation of arm swelling had been assessed in this department in a previous study of arm morbidity after axillary node sample or clearance in patients undergoing mastectomy; there was a significant difference between the treatment groups[14]. Although around 20 per cent experienced interference with daily activities, it would require a huge trial to detect differences between groups. Objective assessment, especially with preoperative and serial post-treatment measurements, is a more powerful way of detecting treatment differences in arm swelling. The present study showed a complex pattern of changes. Patients who had a node sample alone had a minor degree of morbidity lasting up to 6 months and then returned to normal. Those who had a node sample had some arm swelling but this was less than that following surgical clearance and improved with time. However, the range of shoulder movements was significantly reduced after radiotherapy. Axillary clearance was associated with a slight reduction of abduction and a small, but significant increase in the volume of the arm and the girth of the forearm.

The decision about how to manage the axilla may be influenced by the need to know the total number of nodes involved or the requirement to avoid radiotherapy in some patients. Axillary clearance will then be indicated. The surgical policy of routine axillary sampling, as shown both in this study and the previous trial of sample/clearance after mastectomy[13], did not result in an increase in axillary recurrences compared with that after axillary clearance. There was significantly less morbidity in patients found to be node negative who avoided radiotherapy.

A selective policy has now been adopted in the management of the axilla in patients with operable breast cancer. Patients at high risk of axillary node involvement are scheduled for axillary clearance. Patients at intermediate risk are treated by clearance if radiotherapy is to be avoided or by sample with radiotherapy if found to be node positive. Patients who are at low risk of axillary node involvement undergo a node sample, the majority of whom can thus avoid radiotherapy.

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Original article

Mutations of the cationic trypsinogen gene in patients with hereditary pancreatitis

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Background: Hereditary pancreatitis has been shown to be caused by one of two mutations (R117H and N21I) of the cationic trypsinogen gene (*PRSS1*). Families with hereditary pancreatitis in the north of England were investigated for these mutations. The clinical features associated with each mutation were compared.
Methods: In individuals from nine families with hereditary pancreatitis, DNA was screened for the R117H and N21I mutations. All five exons of the cationic trypsinogen gene were also sequenced to search for additional mutations. Haplotype analysis was carried out to identify common ancestors. Clinical data were collected.
Results: The R117H mutation was identified in three families and N21I in a further five. The R117H mutation was associated with a more severe phenotype than N21I in terms of mean(s.d.) age of onset of symptoms (8·4(7·2) *versus* 16·5(7·1) years; $P = 0·007$) and requirement for surgical intervention (eight of 12 *versus* four of 17 patients respectively; $P = 0·029$). Haplotype analysis suggested that each mutation had arisen more than once.
Conclusion: Two mutations in the cationic trypsinogen gene cause hereditary pancreatitis in eight of nine families originating in this region. The R117H mutation is associated with a more severe form of the disease in terms of age at onset of symptoms and requirement for surgical intervention.

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Introduction

Hereditary pancreatitis is an autosomal dominant condition with 80 per cent penetrance. It is characterized by recurrent attacks of acute pancreatitis which typically begin in childhood or adolescence. Over a variable period of time the disease progresses to chronic pancreatitis, which may lead to both exocrine and endocrine insufficiency. The risk of pancreatic adenocarcinoma has also been shown to be increased[1].

Hereditary pancreatitis was first reported[2] in 1952, and since then many families have been described. In 1996, one hereditary pancreatitis locus was mapped to chromosome 7q35 in four large families from North America[3–5]. All these families were shown to have a G:A transition in exon 3 of the cationic trypsinogen gene (*PRSS1*)[6]. This alters arginine (CGC) to histidine (CAC) at codon 117 (using the chymotrypsin numbering system). This mutation (R117H) creates a novel recognition site for the restriction endonuclease *Afl*III[6]. More recently a second mutation (N21I), consisting of an A:T transversion in exon 2, has been identified by a number of independent groups. This causes a substitution of isoleucine (ATC) for asparagine (ACC) at codon 21[7–10].

Trypsinogen is a serine protease precursor secreted by the pancreatic acinar cell[11]. It is activated to trypsin within the duodenum by enterokinase, which cleaves an 8-amino acid N-terminal peptide. Trypsin activates a cascade of digestive enzyme precursors. A number of mechanisms exist to prevent or limit inappropriate activation of trypsin within the pancreas before secretion into the duodenum. The R117H mutation is hypothesized to alter a trypsin recognition site which would prevent deactivation of trypsin within the pancreas and so prolong its action[6]. A similar mechanism of action has not been identified for the N21I mutation.

In this study, families with hereditary pancreatitis were investigated for the presence of mutations in the cationic trypsinogen gene (*PRSS1*). The clinical features associated with these mutations were compared.

Patients and methods

Ethical committee approval was obtained and written informed consent was given by all subjects. Families with hereditary pancreatitis were identified either via the Northern Region Genetics Service, the Hepatopancreaticobiliary Surgery Unit at the Freeman Hospital or the Department of Child Health, Royal Victoria Infirmary, Newcastle. Families were included in the study if more than two family members had a confirmed diagnosis of pancreatitis. Diagnosis was made by the visualization of typical changes on computed tomography or endoscopic retrograde cholangiopancreatography in association with a clinical picture of pancreatitis. Venous blood was taken with ethylenediamine tetra-acetic acid as the anticoagulant and DNA was extracted by standard methods.

Identification of R117H

A region of the *PRSS1* gene containing exon 3 was polymerase chain reaction (PCR) amplified, using the reaction conditions and intronic primers published previously[6]. The PCR fragment was digested with *Afl*III. The reaction mix also included a PCR product of exon 37 of the *dystrophin* gene. This includes an invariant *Afl*III recognition site and thus acted as a control for the integrity of the enzyme. The fragments were sized by agarose gel electrophoresis (*Fig. 1*). In cases where a novel *Afl*III site was detected in exon 3 of *PRSS1*, indicating the presence of the R117H mutation, the PCR product was sequenced to confirm the base change.

Identification of N21I

In families in which R117H was not identified, sequencing of all exons of *PRSS1* was carried out. An A : T transversion in exon 2 was found in five families and has been shown to correspond to the N21I mutation described previously. A novel test was developed to screen for this mutation in other family members. It was not possible to carry out an allele specific test directly because *PRSS1* has high homology with other related trypsinogen genes. The N21I mutation alters the sequence to that found in the anionic trypsinogen gene and a further trypsinogen gene, so it was impossible to design primers that would specifically amplify this mutation in *PRSS1*.

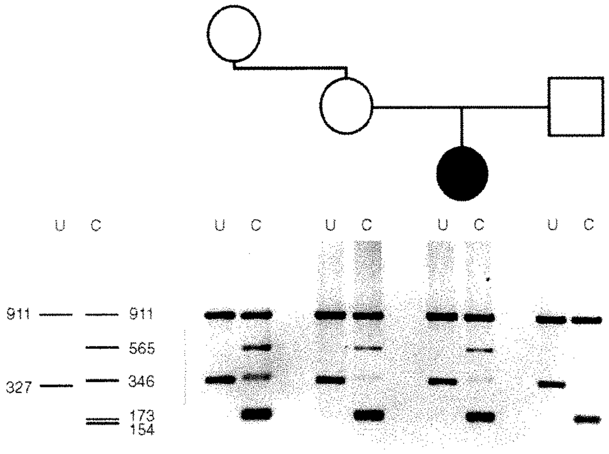

Fig. 1 DNA analysis for the R117H mutation. Gel electrophoresis of polymerase chain reaction (PCR) products before (U, uncut) and after (C, cut) *Afl*III restriction enzyme digestion. The 911-base pair (bp) band corresponds to the *PRSS1* PCR product; *Afl*III digestion creates 565- and 346-bp bands. The 327-bp band is the product using primers from the dystrophin gene with an invariable *Afl*III site, which is used as an internal control to demonstrate the integrity of the enzyme; digestion creates 173- and 154-bp bands. The female individuals are either affected or obligate gene carriers, and are highlighted on *Fig. 3a* within the grey shaded box. DNA analysis shows that each has an *Afl*III site which indicates the presence of a G to A transition at codon 117

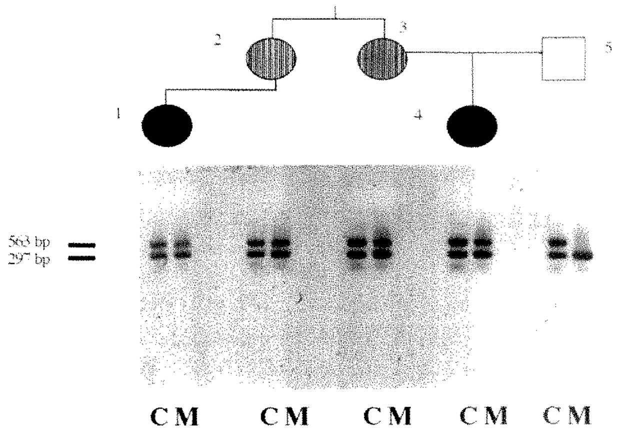

Fig. 2 DNA analysis for N21I mutation. Gel electrophoresis of products from the second polymerase chain reaction (PCR) reactions. Primers were designed to support the reaction only in the presence of either the control (C) or mutation (M) sequence, creating a 563-base pair (bp) product. A clear band from both reactions confirms the presence of the mutation in the heterozygote. The 297-bp product in each lane is created by a pair of control primers and confirms the integrity of the polymerase enzyme used in the PCR reaction. The individuals are those arrowed in *Fig. 3b*. Individuals 1 and 4 have pancreatitis and are shown to carry the mutation on one allele. Individuals 2 and 3 also carry the mutation, but do not have clinical pancreatitis. Individual 5 is the unaffected father of patient 4

Exons 1 and 2 of *PRSS1* were PCR amplified using primers and conditions described previously[9]. The amplified product was separated from genomic DNA by agarose gel electrophoresis and then extracted from the gel. This created a specific PCR fragment for *PRSS1*. A further PCR amplification was then carried out on this purified product

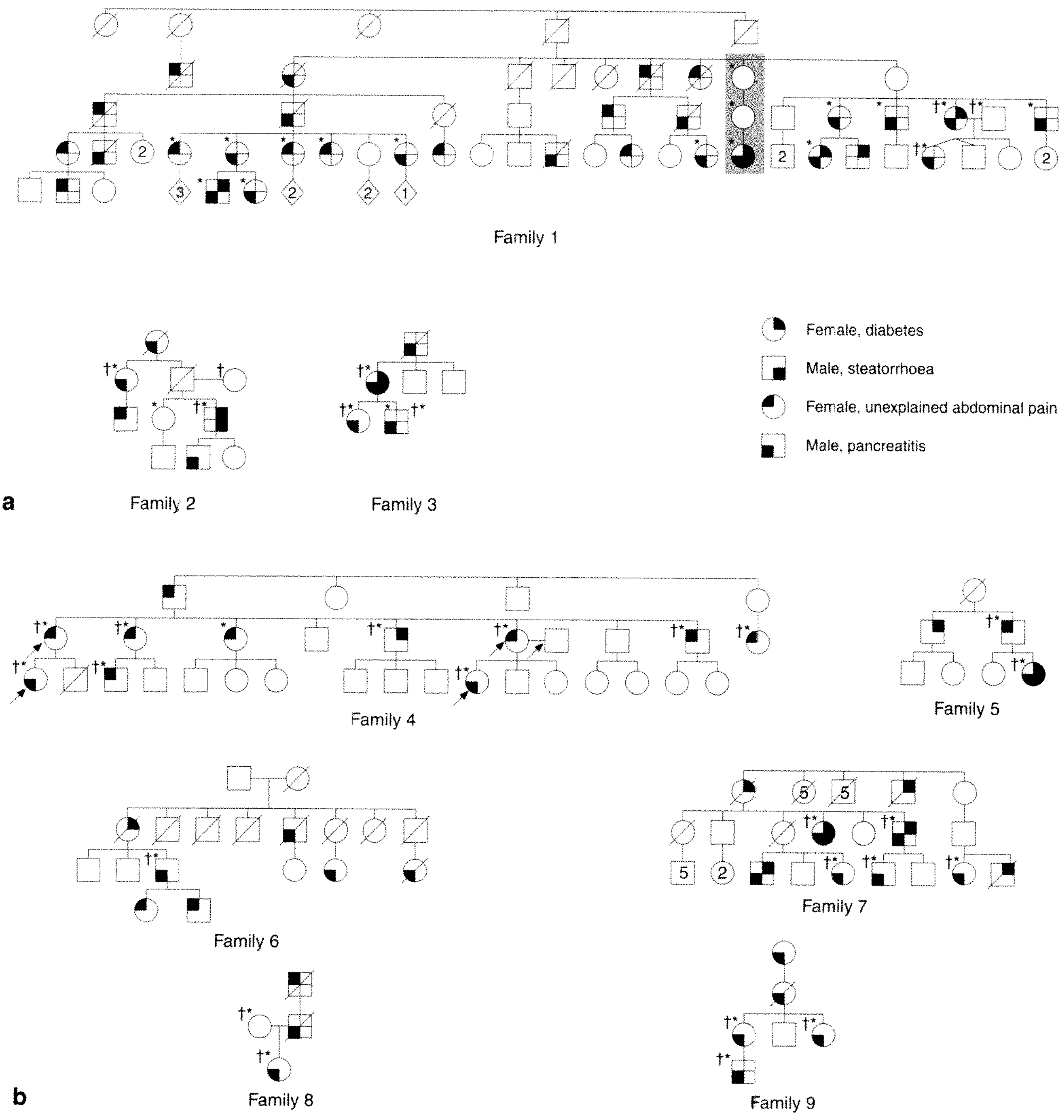

Fig. 3 **a** The pedigrees of three families with hereditary pancreatitis in whom an R117H mutation was identified in affected individuals. The shaded box on family 1 identifies the three female individuals whose DNA results are shown in *Fig. 1*.
b The pedigrees of five families with hereditary pancreatitis in which an N21I mutation was identified, and the remaining family (family 6) in which no mutation was found. The arrows on family 4 identify individuals whose DNA results are shown in *Fig. 2*.
Blood was available from individuals labelled with an asterisk (*) and haplotype analysis was done in those marked with a dagger (†)

using primers designed to support the reaction only in the presence of either the normal or mutation sequence. Primers used were: (5′ normal sequence primer) 5′-AAGATCGTTGGGGGCTACAA-3′, (5′ mutation sequence primer) 5′-AAGATCGTTGGGGGCTTCAT-3′ and (3′ primer for both reactions) 5′-ACAGTTAGCAGAGGTAGAGTG-3′. A second pair of primers was added to each reaction to act as an internal control. These were: (5′ primer) 5′-TCACAGTCACCTCCTCTC-3′ and (3′ primer) 5′-GAGAAGGTGAACAGGTGAG-3′). Cycling conditions consisted of an initial denaturation at 94°C for 4 min; 30 cycles at 94°C for 1 min, 60°C for 1 min, 72°C for 1 min; with a final elongation step of 72°C for 10 min. Bands were visualized following agarose gel electrophoresis, where a clear band from both reactions confirmed the presence of the mutation in a heterozygous individual (*Fig.* 2). The mutation was confirmed in each case by sequencing, using a specifically designed primer (5′-GAAAGCAATCACAGGCTG-3′).

In families where either R117H or N21I was identified, haplotypes were determined for the individuals indicated in *Fig. 3*, to examine the possibility that apparently unrelated families shared a common ancestor. Haplotype analysis was carried out using three STR (short tandem repeat) markers (R-G, R-I and R-M, as described by Charnley *et al.*[12]) lying upstream of the *PRSS1* gene and closely linked within a 680-kilobase region.

Where possible, full clinical details were recorded using a structured interview and from review of the hospital notes. This included details of age of onset of symptoms and the clinical course of the illness, including details of any pancreatic surgery carried out. A detailed alcohol consumption history was obtained. Details of any provoking factors identified by the patients and of any complications, including exocrine and endocrine failure, were recorded.

Statistical analysis was carried out with Student's *t* test or Fisher's exact test as appropriate.

Results

Nine families fulfilled the criteria of having more than two family members with a confirmed diagnosis of pancreatitis (*Fig. 3*). Blood was available from 34 affected individuals, and full clinical details were available in 29; only limited clinical data were available in the remaining five. One family (family 1 in *Fig. 3*) was previously reported in 1975, which was before the advent of molecular investigation[13,14]. A genealogical link was established between two families (families 5 and 7) but, despite detailed questioning, none of the other families was believed to be related and none shared common family names.

Distribution of the two mutations

The R117H mutation was identified in all affected members of three of the families (families 1, 2 and 3). DNA sequencing confirmed the presence of a G:A transition mutation. The N21I mutation was demonstrated in a further five families (families 4, 5, 7, 8 and 9). In the remaining family (family 6), no mutations were demonstrated in any of the five exons of *PRSS1*. Only the two described mutations were identified.

Haplotype analysis

Two different haplotypes were identified in the three families with the R117H mutation. Families 1 and 3 shared a haplotype, suggesting a common ancestor; in family 2 a different haplotype was inherited alongside the mutation. Two further different haplotypes were identified in the five families with the N21I mutation. Families 4, 5, 7 and 8 shared a haplotype, again suggesting common ancestry, whilst family 9 had a unique haplotype. In the remaining family (family 6), DNA was not available from sufficient family members to confirm or disprove linkage to *PRSS1*.

Clinical data

Of the 29 patients for whom full clinical data were available, 12 carried R117H; a further 17 carried N21I. The R117H and N21I groups were compared. Mean(s.d.) age at onset of symptoms of pancreatitis was lower in the R117H group (8·4(7·2) *versus* 16·5(7·1) years; $P = 0{\cdot}007$) and more patients with R117H had developed symptoms by the age of 20 years (89 *versus* 64 per cent). More patients with R117H required surgical intervention (eight of 12 *versus* four of 17; $P = 0{\cdot}029$) and this tended to be at an earlier age (mean(s.d.) 21·6(15·4) *versus* 31·5(13·1) years; $P = 0{\cdot}15$). There was a tendency for more patients with R117H to develop exocrine failure (seven of 12 for R117H *versus* five of 17 for N21I; $P = 0{\cdot}12$), although mean(s.d.) age at onset of exocrine failure was similar in both groups (24·9(16·5) *versus* 32·3(16·3) years respectively; $P = 0{\cdot}26$). The incidence and age at onset of endocrine failure (insulin-dependent diabetes mellitus) was similar in both groups. Patients in both groups identified alcohol as a provoking factor for their symptoms, but none had a history of excessive alcohol intake.

Discussion

Hereditary pancreatitis is identical to other forms of pancreatitis in terms of clinical presentation and radiological and histopathological features[15]. Premature activation of trypsinogen or failure of trypsin breakdown within the pancreas may cause some cases of sporadic pancreatitis.

Two mutations in the cationic trypsinogen gene have been shown to cause the disease in eight of nine affected families in this study. There is wide phenotypic variability associated with both mutations even within the same family. In some patients diabetes with or without exocrine failure was the only presenting symptom. Environmental and/or other genetic factors responsible for the heterogeneity have not been identified. Clinicians should have a high index of suspicion for *PRSS1* mutations if relatives have even mild symptoms of pancreatic disease[16].

Delay in diagnosis, often for many years, has been shown to occur frequently in hereditary pancreatitis[17]. Genetic testing allows an unequivocal diagnosis to be made rapidly, even in relatives who have vague symptoms. In practice, this information is helpful in allowing individuals to make informed lifestyle choices. When counselling an asymptomatic individual found to have a mutation, it is impossible to say whether they will develop the disease because the mutation is only 80 per cent penetrant. The majority of affected individuals will, however, develop symptoms before the age of 20 years[14].

The R117H phenotype is more severe than that associated with N21I, a finding supported by others[7]. Previous work[14], predating genetic testing, demonstrated two peak age ranges for onset of symptoms. This present study suggests that the earlier peak (at age 3–7 years) is accounted for largely by patients with R117H, whilst the later peak (at ages 16–19 years) is found mainly in patients with N21I.

There remains a proportion of patients with hereditary pancreatitis in whom no mutations in *PRSS1* have been demonstrated[1] and it has been suggested that a second locus may exist. In this study no mutations were found in one family. In the absence of conclusive proof that the disease in this family was linked to *PRSS1*, more exhaustive investigation of the gene was not carried out.

Using markers closely linked to the gene, common haplotypes were identified in two of the three families with R117H and in four of the five families with N21I, indicating that distant common ancestors are likely to have existed for these families. Each mutation, however, has been identified in unrelated families. This suggests that each mutation may have occurred more than once but, in the absence of data from a flanking marker downstream from *PRSS1*, a single recombination event could possibly explain different haplotypes occurring in relation to each mutation.

Hereditary pancreatitis may predispose to pancreatic adenocarcinoma[1] but an underlying pathogenic mechanism has not been clearly established. Of the nine families in this study, two individuals from separate families are known to have died from carcinoma of the pancreas. It has been suggested that the relative risk of developing pancreatic cancer is up to 42-fold in patients with hereditary pancreatitis, that it tends to occur at an earlier age, and that it is more likely in patients with a long history of symptoms[1,18]. At present, no screening technique for pancreatic cancer is recommended. If patients with hereditary pancreatitis require pancreatic surgery, it is reasonable to suggest that they should undergo total pancreatectomy, particularly if they have a long history of symptoms.

This preliminary study has shown that two mutations in the *PRSS1* gene may be responsible for a significant proportion of cases of hereditary pancreatitis. These mutations can be detected rapidly and are of benefit when counselling other family members.

Acknowledgements

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Original article

Role of relaparoscopy in the management of minor bile leakage after laparoscopic cholecystectomy

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Background: Bile leakage in the absence of major ductal injury may occur from the liver bed or from the cystic duct remnant after cholecystectomy. The early limitations of minimally invasive surgery led to reliance on endoscopic methods to manage this complication. However, repeat laparoscopy permits drainage of the bile collection and direct control of the site of leakage in selected situations.
Methods: Details of 15 patients with bile leakage after laparoscopic cholecystectomy were recorded prospectively and are reviewed.
Results: Postoperative bile leakage occurred after 15 (0·8 per cent) of 1779 laparoscopic cholecystectomies. Two patients with bile in drainage fluid had spontaneous resolution. Ten patients with a subvesical duct leak had repeat laparoscopy. The leak was successfully controlled by suturing in eight patients, and by a laparoscopically placed drain in two. One patient required a subsequent laparotomy for a loculated pelvic collection. Three patients had cystic duct stump leakage. This was managed successfully by laparoscopy in one case but required endoscopic management in two.
Conclusion: Laparoscopy is useful in the management of minor bile leaks after laparoscopic cholecystectomy. Selection of appropriate patients relies on a characteristic clinical presentation after an otherwise uncomplicated cholecystectomy.

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Introduction

In the absence of any major duct injury, bile leakage after open cholecystectomy occurs in 0·3–2·4 per cent of cases[1,2], although an incidence of up to 9 per cent has been recorded[3]. It has been suggested that this rate is increased after laparoscopic cholecystectomy[4], although the incidence in large prospective series is similar, with rates between 0·4 and 2 per cent reported[2,5,6].

Bile leaks may arise from a subvesical duct (of Luschka), a cystic duct stump or an aberrant sectoral duct. They may result in a localized collection, biliary peritonitis or, in the presence of a drain, a biliary fistula. Although these 'minor' bile leaks are not a new problem, many recent articles have suggested that endoscopic retrograde cholangiography (ERC) for diagnosis and management is the appropriate form of therapy[7–10]. ERC has associated morbidity and mortality[11], and frequently needs to be combined with further procedures[12]. Repeat laparoscopy can identify and deal with the site of leakage, and adequately drain the bile collection that is responsible for the patient's symptoms.

The aim of this study was to review a series of bile leaks occurring after laparoscopic cholecystectomy performed in a single specialist surgical unit where repeat laparoscopy was used as the primary therapeutic intervention.

Patients and methods

All bile leaks occurring after laparoscopic cholecystectomy were recorded prospectively from 1990 until July 1998. The case records, iminodiacetic acid (HIDA) scans and operation reports were reviewed retrospectively for each patient.

Cholecystectomy was performed using a four-port technique and standing on the patient's left side. A selective approach to operative cholangiography was adopted[13]. Minimal diathermy was used to dissect Calot's triangle and a diathermy spatula was used to dissect the gallbladder from the liver bed. Drainage with a closed suction drain was used routinely, usually placed in the subphrenic space[14].

When the probability of a retained stone or major ductal injury is low, the preferred method for management of symptomatic postoperative bile leakage is laparoscopy.

However, management of this complication has sometimes been influenced by the availability of imaging techniques and the need to operate out of hours. Supplementary investigations and ERC, carried out by the authors, were used more frequently earlier in the series. The current approach to patients who develop symptoms of a bile leak after an otherwise uncomplicated laparoscopic cholecystectomy performed by the authors is shown in *Fig. 1*. Patients who are referred from other centres, those with a raised level of bilirubin or other reason for suspecting a retained common bile duct stone, such as an abnormal intraoperative cholangiographic finding, or those with a high-output biliary fistula (greater than 400 ml daily) are investigated primarily with ERC.

The technique of relaparoscopy involves establishment of ports through their previous sites, aspiration of the bile collection, elevation of the liver, and irrigation. After any adherent omentum has been carefully separated from the gallbladder bed, the site of the leak is usually visualized readily with the magnification afforded by the laparoscope. A discrete hole can be seen, often seen as a side-hole in a ductule running either in the centre of the gallbladder bed or at the lateral peritoneal reflection. If bile staining makes identification of the leak difficult, a gauze swab is passed down a 10-mm port and applied to the dry liver bed to identify the site of leak. Laparoscopic suture of the site of leakage with 3/0 polyglactin and drainage with a low-suction drain completes the procedure. An additional 5-mm port placed in the left upper quadrant for the needle-holder may facilitate suturing.

Results

A total of 1779 laparoscopic cholecystectomies was attempted during this period, with a conversion rate of 3·2 per cent. A biliary leak occurred in 15 patients (0·8 per cent) after operation. During this time two patients (0·1 per cent) with Mirrizzi syndrome had a major bile duct injury during laparoscopic cholecystectomy. One injury, a lateral incision of the common bile duct for the cholangiogram, was recognized and repaired during operation. The other patient presented with jaundice as a result of a clip occluding the common hepatic duct, which was repaired at subsequent laparotomy. Twelve patients were referred from other centres for repair of major duct injuries.

The management of the 15 patients presenting with a bile leak is shown in *Fig. 2*. Of the patients presenting with a minor biliary leak, two had a small amount of bile in the drain after operation which resolved spontaneously and the site of leak was never identified.

Three patients were leaking from the cystic duct stump, one secondary to retained stones. This patient had an abnormal intraoperative cholangiogram and a raised bilirubin level after operation, and was managed successfully with ERC and stenting. Two patients with minimally abnormal liver function and normal intraoperative cholangiograms had repeat laparoscopy. One patient had an identifiable leak coming from below the clip on the cystic duct; this was sutured laparoscopically and the patient made an uneventful recovery. The other patient had no recognizable site of leak and a drain was placed. A low-output biliary fistula resulted that reduced in volume. The drain blocked on day 5 and ERC was done because of continued pain on day 7. This showed a leak from the cystic duct, just below

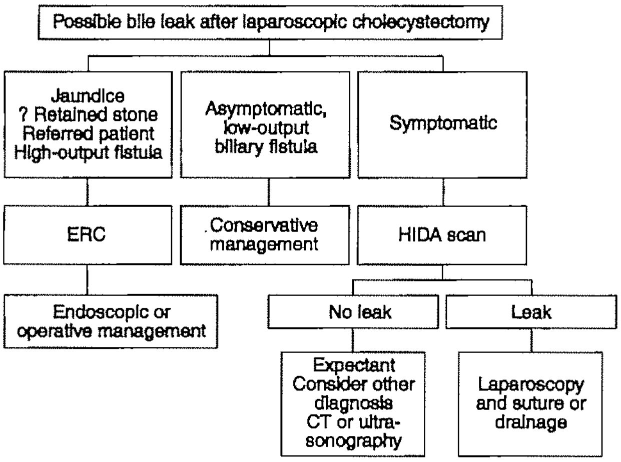

Fig. 1 Current management of biliary leak after laparoscopic cholecystectomy. CT, computed tomography; ERC, endoscopic retrograde cholangiography; HIDA, iminodiacetic acid

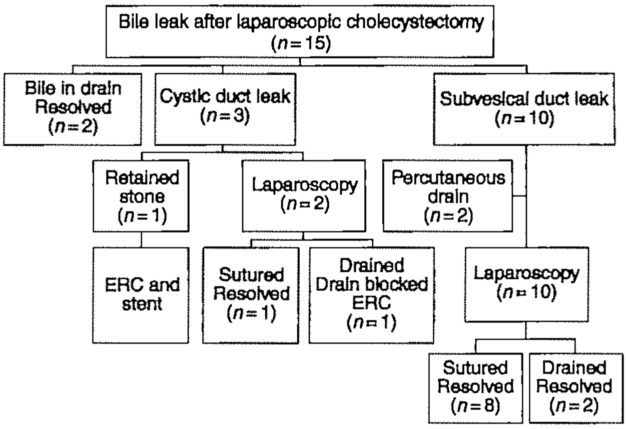

Fig. 2 Flow chart of patient outcome. ERC, endoscopic retrograde cholangiography

the clips. There was no common duct stone, and the patient had a stent placed with resolution of symptoms.

Of the ten patients with leaks from the gallbladder bed, one presented with bile in the drain after operation and nine presented symptomatically. Three had intraoperative cholangiograms, which were normal. The presenting symptom of bile leak was right upper quadrant pain in all patients, sometimes referred to the shoulder and frequently associated with nausea. Two patients had a mild leucocytosis and seven had mild abnormalities of liver function, most frequently a slightly raised γ-glucuronyltransferase concentration. Only one patient had an increased level of bilirubin, but this was unchanged from the preoperative level and was secondary to haemolysis.

There were two modes of presentation. Three patients had evidence of a bile leak from the time of the operation. This included two patients with excessive postoperative pain and one patient with bile in the drain, in whom laparoscopy was performed after the drain became blocked on the seventh postoperative day. The other seven patients were well and had been discharged, or were close to discharge, from hospital. They had sudden onset of right upper quadrant pain at a median of 3 (range 2–5) days after operation.

The mean volume of bile found at laparoscopy was 205 (range 50–400) ml. The site of leakage was identified in eight of ten patients at the initial laparoscopy and sutured, with immediate resolution of the leak. Two patients were treated by drainage alone; both leaks resolved after 5 days. However, one of these patients required laparotomy 7 days later because of loculated pelvic collections resulting in ongoing sepsis. When the omentum was stripped from the liver bed in this procedure, the site of leak was re-established, identified and sutured. Thus the exact site of leakage from the gallbladder bed was identified in nine patients. The leaks occurred from two distinct areas: four leak sites occurred in a line running down the centre of the gallbladder bed; the other five sites were along the lateral peritoneal reflection.

Two patients had percutaneous drains inserted under computed tomographic guidance as a preliminary procedure; however, ongoing pain and bile leakage after 5 days led to laparoscopy. The median time to laparoscopy after cholecystectomy was 5·5 (range 3–14) days. The median length of stay after the repeat laparoscopy was 4 days. All patients were seen at follow-up 2–6 weeks after operation. Results of liver function tests, obtained in six patients, were normal. No patient has developed evidence of subsequent biliary problems over a mean follow-up of 2·5 years.

The investigations performed to diagnose the bile leaks varied. Initially ERC and computed tomography (CT) or ultrasonography were used. ERC was performed in two patients early in the series. In one it failed to demonstrate a leak and the patient went on to have CT and percutaneous drainage. The patient had persisting pain after 5 days, and had laparoscopy and suture of the duct in the liver bed with rapid resolution of symptoms. The other patient had a nasobiliary tube inserted but pulled this out later the same day and went on to laparoscopy. HIDA scans were increasingly used, and were undertaken in six patients. They provided a sensitive investigation in all patients for demonstration of bile leakage. The leak was apparent 10–20 min after commencement of the scan with radiotracer accumulating in the right subhepatic space, clearly separate from the liver. One patient had two scans. The initial scan was negative. At this time a percutaneous drain had been inserted and the patient was pain free. Clinically it was considered that the leak had resolved spontaneously. However, pain and bile drainage recurred 48 h later; the HIDA scan was repeated and confirmed a bile leak. The patient opted for repeat laparoscopy rather than expectant management.

Overall, 13 of the 15 patients required intervention for resolution of the bile leak. One with a retained common bile duct stone had ERC and biliary stenting. Twelve patients had laparoscopy, and this was successful at controlling the leak in 11, the other patient requiring ERC and stenting.

Discussion

This study identified 15 patients presenting with a bile leak after an otherwise uncomplicated laparoscopic cholecystectomy and has demonstrated that laparoscopy in selected patients allows control of the source of the leak as well as drainage of the bile collection. Laparoscopy has been used infrequently in other series to treat bile leaks, with limited success. Sefr *et al.*[15] performed laparoscopy, diathermy to the site of bile leakage and drainage in three patients, with resolution over 5, 6 and 9 days. The benefit of the laparoscopy in these patients was probably the accurate placement of a drain. Brooks *et al.*[16] performed laparoscopy in three patients with drainage only. There was resolution of leakage in two patients by 7 days, the third patient requiring ERC and sphincterotomy. Albasini *et al.*[17] performed laparoscopy and suture in one patient, although it appears that bile continued to drain and a percutaneous drain was subsequently used.

Most of the leaks seen in this series were from subvesical ducts. These 'ducts of Luschka', which occur in 30–50 per cent of the population, are found most frequently in the centre of the gallbladder bed and are at risk of division during dissection of the gallbladder from the liver bed by diathermy[3,4,18]. Leaks usually arise from a side-hole, which makes them unsuitable to clip, with laparoscopic suturing being necessary for closure. Laparoscopic drainage is likely to be successful, although often the patience of both the surgeon and patient will be tested waiting for resolution. In contrast to percutaneous drainage, the laparoscopic drain is sited close to the leak and the loculated bile collection is aspirated with adequate suction before drain placement. Dissection of the gallbladder from the liver is more precise during laparoscopic cholecystectomy, a similar amount of diathermy is used to that for open cholecystectomy and, apart from awareness of these ducts during dissection, there appears to be little that could have been done to prevent injury. Recognition of a small bile leak from the liver bed enabled immediate intraoperative control for four other patients over the last 2 years of the study.

In contrast, leakage from the cystic duct, which is the most common site of 'minor' bile leakage after laparoscopic cholecystectomy in large multicentre series[6], should be preventable with the use of pre-tied loops or laparoscopic suture for difficult cystic duct closures. If a leak occurs from a cystic duct that was difficult to close at the initial laparoscopy, repeat laparoscopy is not likely to be helpful. Endoscopic stenting will decrease intrabiliary pressure and permit the leak to close[12].

If bile appears in drainage fluid after operation, the natural history after open cholecystectomy is for the leak to resolve[3]. Unfortunately bile may not appear in the drain[19,20], and the results of the present series suggest that onset of bile leakage may be a delayed occurrence in some patients when the drain has already been removed.

There have been numerous recent articles advocating ERC for diagnosis and endoscopic management of postoperative bile leaks with stenting or nasobiliary drainage[7–10]. Some authors have suggested that failure to perform ERC when a minor bile leak becomes evident denies the patient 'conservative treatment'[21]. ERC and sphincterotomy carries a morbidity rate of 5 per cent and a mortality rate of 1 per cent, which is higher than that for a laparoscopic procedure in what is usually a group of relatively young and healthy patients[11,22].

For a patient presenting with symptoms of a bile leak following an otherwise uneventful laparoscopic cholecystectomy, repeat laparoscopy is a valid and useful form of treatment providing there is no jaundice or suspicion of a retained common bile duct stone. Repeat laparoscopy is not recommended where there is a potential major duct injury.

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Original article

Role of biliary scintiscan in predicting the need for cholangiography

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Background: Currently used predictors for bile duct calculi in patients undergoing cholecystectomy have low specificity resulting in unnecessary cholangiograms being performed. The role of biliary scintiscan in predicting the presence of bile duct calculi was assessed.
Methods: Seventy-five patients with symptomatic gallstone disease were studied prospectively regarding the value of a history of jaundice or acute pancreatitis, raised serum bilirubin and serum alkaline phosphatase levels, and visualization of stones or presence of dilated bile ducts on ultrasonography (standard criteria) in detecting bile duct calculi. Results of biliary scintiscan were evaluated against a combination of standard criteria. The 'gold standard' for evaluation was endoscopic or peroperative cholangiography.
Results: Biliary scintiscan had a higher sensitivity and specificity (93 and 94 per cent) than a combination of the above standard and modified predictors for biliary calculi (89 and 71 per cent). A combination of ultrasonography and selective use of scintiscan, in the absence of bile duct dilatation only, had higher values (96 and 98 per cent).
Conclusion: A combination of ultrasonography and biliary scintiscan can accurately predict bile duct calculi and could be used as a guide for selective cholangiography.

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Introduction

Prediction of common bile duct (CBD) pathology in patients with gallstones relies on a history of jaundice or acute pancreatitis, abnormal liver biochemistry and ultrasonographic demonstration of biliary tract dilatation[1–6]. However, in the absence of these criteria 3–12 per cent of patients have been found to harbour unsuspected CBD calculi[1,5,7–10]. Furthermore these criteria have a low positive predictive value, so selective cholangiography (either endoscopic or peroperative) performed on the basis of these parameters results in unnecessary cholangiography in about half (29–72 per cent) of the patients[2,5,9,11–15]. There is a need for an investigation that can predict the likelihood of CBD pathology with a high degree of reliability and act as a guide to performing selective preoperative endoscopic retrograde cholangiography (ERC) or peroperative cholangiography (POC).

Biliary scintiscan allows physiological evaluation of the biliary tree. It has been used as an effective screening test in patients suspected of having biliary duct problems after cholecystectomy[16] as well as following liver transplantation[17]. It detects early or partial CBD obstruction before the development of bile duct dilatation or jaundice[18]. However, its value in determining the need for cholangiography for biliary calculi has not been evaluated adequately. This prospective study evaluated the role of biliary scintiscan in predicting the presence of obstructive bile duct pathology in patients with gallstones undergoing cholecystectomy, and therefore its efficacy, compared with currently used criteria, as a guide to selective cholangiography.

Patients and methods

This prospective study was carried out in a single surgical unit in a tertiary referral centre and included 75 consecutive eligible patients with symptomatic gallstone disease. Patients experiencing an attack of acute cholecystitis, acute pancreatitis or cholangitis were excluded. A detailed history was taken regarding past episodes of jaundice or acute pancreatitis. Biochemical investigations at presentation were considered abnormal when the serum bilirubin level was more than 1·0 mg/dl (17 µmol/l) and the serum alkaline phosphatase concentration exceeded 91 units/l. Ultrasonographic criteria used for suspecting bile duct pathology were the visualization of a CBD stone, presence of intrahepatic bile duct dilatation, or common hepatic duct or CBD size greater than 7 mm[19].

Biliary scintiscan was performed using intravenous injection of 5 µCi ^{99m}Tc-radiolabelled mebrofenin. Images were recorded with a γ camera (Elscint SPX-4; Elscint, Haifa, Israel) with an all-purpose low-energy collimator at 5, 15, 30, 60 and 120 min; delayed and right lateral images were taken when required. After 2 h the study was continued to evaluate gallbladder function. The study was evaluated by a blinded examiner. Criteria for CBD obstruction were absent gut tracer entry at 60 min, delayed biliary duct to bowel transit time (interpreted as build-up of biliary tree tracer activity for over 60 min) and a prominent ductal pattern that did not wash out by 2 h[18].

Preoperative ERC was performed whenever possible in patients with a high index of suspicion for CBD stones based on clinical, biochemical and ultrasonographic criteria. The remainder underwent POC. The patients found to have CBD calculi were subjected to endoscopic sphincterotomy or open surgical exploration of the CBD. The findings at ERC and/or POC and those of CBD exploration were taken as the 'gold standard' for evaluating the predictive value of each parameter. All investigations were performed within 2 weeks of surgery or ERC. Informed consent was obtained for all procedures.

The results were analysed by calculating the sensitivity, specificity, and negative and positive predictive values of each criterion. The optimal cut-off value for a parameter to detect CBD pathology independently was assessed using receiver–operator characteristic curve analysis[20]. The risk of harbouring a CBD stone was then calculated with different combinations of parameters. The predictive value of all the standard criteria in combination was then compared with that of biliary scintiscan alone. Statistical analysis was done using χ^2 test or Fisher's exact test where applicable. $P < 0·05$ was taken as significant.

Results

Of 75 patients, 27 (36 per cent) had bile duct pathology that required treatment The high incidence of bile duct pathology probably reflects a referral bias. The mean(s.d.) age of the population was 46(13) years. Forty-six patients were women. The clinical characteristics and results of investigations in patients with and without bile duct pathology are presented in *Tables 1* and *2*.

Table 1 Clinical and investigative findings in patients with and without bile duct pathology

	Bile duct pathology (*n* = 27)	No bile duct pathology (*n* = 48)
History of jaundice	19	11
History of acute pancreatitis	1	4
Serum bilirubin > 1 mg/dl	16	3
Serum alkaline phosphatase > 91 units/ml	18	14
Dilated bile duct on ultrasonography > 7 mm	17	2
Bile duct stone on ultrasonography	12	0
Abnormal bile duct on ultrasonography	18	2
Positive standard criteria	24	25
Delayed tracer transit on scintiscan	25	3

Table 2 Clinical and investigative findings in patients with and without bile duct pathology using the modified criteria

	Bile duct pathology (*n* = 27)	No bile duct pathology (*n* = 48)
Jaundice within the past 3 months	17	4
Serum bilirubin > 1 mg/dl	16	3
Serum alkaline phosphatase > 125 units/ml	17	9
Dilated bile duct on ultrasonography > 9 mm	17	0
Bile duct stone on ultrasonography	12	0
Abnormal bile duct on ultrasonography	18	0
Positive modified criteria	24	14
Delayed tracer transit on scintiscan	25	3

Results of selective cholangiography

Twenty-six patients with a high index of suspicion for CBD calculi were subjected to preoperative ERC. Two cholangiograms failed, five were normal, 18 revealed CBD calculi and one showed papillary stenosis with a dilated CBD but no bile duct calculi (*Fig. 1*).

POC was performed in the remaining 51 patients (including the two in whom ERC failed) and was successful in 49 (96 per cent); of these only seven cholangiograms were abnormal. The two patients who had failed POC later presented with abdominal pain and underwent postoperative ERC, at which one was found to harbour a solitary stone in a bile duct of normal diameter (*Fig. 1*).

Analysis of predictive factors

A history of jaundice was present in 30 patients of whom 19 ultimately were shown to have bile duct stones. A recent attack of jaundice within the previous 3 months was a better predictor of CBD stones than a more remote history

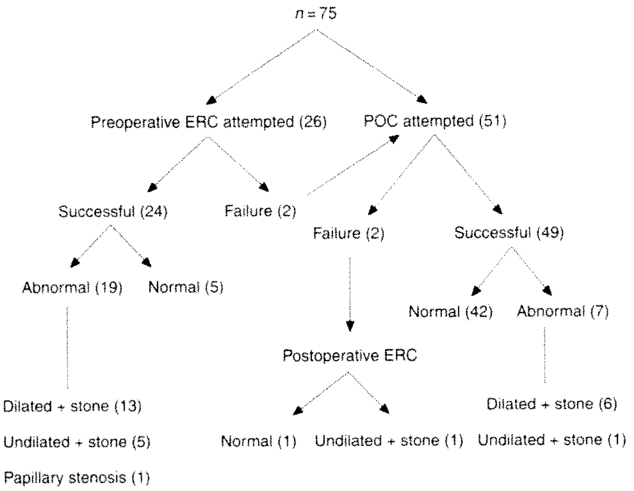

Fig. 1 Flow chart showing results of cholangiography. ERC, endoscopic retrograde cholangiography; POC, peroperative cholangiography

Table 3 Results of different parameters in predicting the presence of bile duct pathology

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Common bile duct >9 mm on ultrasonography	63	100	100	83
Common duct stone on ultrasonography	46	100	100	76
Abnormal bile duct on ultrasonography	67	96	90	84
Abnormal biliary scintiscan	93	94	89	96
All standard criteria combined	89	48	49	89
Modified standard criteria	89	71	63	92
Ultrasonography + scintiscan	96	98	96	98

PPV, positive predictive value; NPV, negative predictive value

(*Tables 1* and *2*). Of five patients with a history of acute pancreatitis, only one had bile duct stones.

A raised serum bilirubin level was found to be a highly specific (94 per cent) indicator of bile duct stones although its sensitivity was low (59 per cent). Serum alkaline phosphatase concentration, at the standard laboratory value of 91 units/ml, yielded concentration intermediate sensitivity (67 per cent) and specificity (71 per cent). Receiver–operator characteristic curve analysis[20] showed the optimal cut-off level to be 125 units/ml.

A dilated bile duct on ultrasonography was highly specific (96 per cent) in predicting bile duct pathology but the sensitivity was only 63 per cent. The specificity and positive predictive value could be raised to 100 per cent with no fall in sensitivity by raising the upper limit of normality from 7 to 9 mm (*Table 3*). Ultrasonography detected stones in only 12 of 26 patients yielding poor sensitivity (46 per cent) but high specificity (100 per cent).

Biliary scintiscan had a high sensitivity and specificity (93 and 94 per cent respectively). Of the 28 abnormal scintiscans only three were false positive (positive predictive value 89 per cent). When all the standard criteria were considered together and compared with nuclear imaging, three of 27 patients harbouring bile duct pathology were missed by all the established parameters whereas two were missed by scintiscanning alone. The positive predictive value of biliary scintiscan was significantly higher than that of a combination of the standard criteria (89 *versus* 49 per cent; $P = 0.0004$), even when the more stringent modified criteria were used (89 *versus* 63 per cent; $P = 0.016$) (*Table 3*).

Of the seven patients with CBD stones but normal bile duct size (less than 7 mm), scintigraphy showed tracer hold-up in six; the remaining patient was missed by all the non-invasive modalities used. Ultrasonography detected stones in only one of these seven patients ($P = 0.015$)

Discussion

It is important to know whether a patient who is to undergo cholecystectomy harbours bile duct pathology. With the increasing popularity of laparoscopic cholecystectomy, the use of preoperative endoscopic duct clearance has risen to maintain the benefits of minimally invasive therapy[1]. With the dogma of routine cholangiography being challenged and the hazards of routine ERC realized, the majority of surgeons now recommend selective cholangiography[1–4,7,8,12–15]. The criteria for selection of patients for cholangiography have to be stringent. The parameters must be sensitive enough to prevent missing patients with bile duct stones, and must also a have high positive predictive value so that many unnecessary cholangiograms are not performed.

The commonly used predictors of bile duct calculi are a history of jaundice or acute pancreatitis, abnormal liver biochemistry and sonographic suspicion of choledocholithiasis. The predictive value of a raised serum alkaline phosphatase level, hyperamylasaemia and a history of pancreatitis has been demonstrated to be low in other series[4,6,14,21], as was seen in the present study. About 30 per cent of patients with CBD stones have normal liver biochemistry[15,21,22]. Duct diameter on ultrasonography correlates with the probability of finding a stone[3,21,23], and duct diameter ranging from more than 5 mm to 12 mm has been taken as a good predictor of CBD stones. In the present study, a duct diameter of more than 9 mm proved to be optimal. Ultrasonography, although highly specific[12,14,19], when the bile duct is dilated or a CBD stone is seen, has a low sensitivity, particularly in the absence of ductal dilatation[4,5,15,18], as was the case in this study (*Table 3*); it cannot therefore be used as the sole guide.

Biliary scintiscan has rarely been used as a predictor of CBD stones. Lecklitner *et al.*[24] obtained excellent results, proving it to be sensitive (97 per cent) as well as accurate (93 per cent). Zeman *et al.*[18] concluded that biliary scintiscan was more sensitive than ultrasonography (98 *versus* 78 per cent) and equally specific (85 *versus* 86 per cent). The results of this study compare favourably, with a high sensitivity (93 per cent) and specificity (94 per cent). The chance that a patient with normal scintigraphic tracer transit might still harbour a CBD stone is less than 5 per cent. In an undilated system scintigraphy was far superior to ultrasonography in predicting the presence of bile duct calculi in this series.

The specificity and positive predictive value of biliary scintiscan was significantly higher than that of the combination of either standard ($P = 0{\cdot}0004$ and $P = 0{\cdot}016$ respectively) or modified standard criteria. If biliary scintiscan alone had been used as a guide to selective cholangiography, only three (11 per cent) of 28 cholangiograms would have been performed unnecessarily. This is far less than the 29–72 per cent incidence of unnecessary cholangiograms reported in the literature with use of standard predictors[2,5,9,11–15]. The results of nuclear scanning can be improved further with more rigorous techniques as shown by Krishnamurthy *et al.*[25]. Poor results obtained by some studies evaluating scintigraphy[15] can be explained on the basis of faulty criteria used for interpretation of the images.

An abnormal ultrasonographic scan has the highest specificity of all the predictive parameters, so scintigraphy is not necessary in these cases. In patients with a normal ultrasonographic scan, biliary scintiscan would accurately predict those harbouring bile duct stones. In the present study, if this policy of selective cholangiography had been followed, based on 57 scintiscans, only 27 cholangiograms would be have been necessary, one of which would have been normal. In only one patient would stones have been missed. Scintiscanning is less than one-third the cost of ERC (1050 Rupees (approximately £15) *versus* 3500 Rupees (£50)) and has the additional advantage of being a complication-free outpatient procedure. It is also more economical than magnetic resonance cholangiography (5000 Rupees (£71)) which has recently been shown to be an accurate investigation for detecting bile duct calculi[26], although doubt has been cast on its ability to visualize calculi in ducts less than 6 mm in size[27].

The strength of this study is that it is prospective and that all patients underwent cholangiography. A limitation of other studies performing selective cholangiography[4,5,12,15] is that the incidence of CBD stones in patients not subjected to cholangiography was not known, so the true sensitivity of each parameter could not be determined.

In the presence of a normal ultrasonographic scan and scintiscan, the chance of harbouring a CBD stone is low and cholangiography can be safely avoided. It is therefore concluded that biliary scintiscan findings can be used as a guide for selective preoperative ERC or POC in patients undergoing cholecystectomy.

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Original article

Spontaneous carotid artery aneurysms

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Background: Spontaneous carotid artery aneurysms are infrequently reported, and are almost always non-atherosclerotic.

Methods: The records of 29 patients with a spontaneous carotid aneurysm treated in an academic vascular unit between 1990 and 1998 were reviewed.

Results: All 29 patients were black South Africans; three had bilateral aneurysms. There were 24 men and five women, of mean age 35 (range 13–62) years. Some 25 aneurysms involved the common carotid artery, 12 of which affected the bifurcation, and seven were located in the internal carotid artery. Twenty-five aneurysms were managed surgically, four of which were ligated owing to sepsis. Histological evaluation showed human immunodeficiency virus-related arteritis in four, tuberculous aneurysms in ten, Takayasu's arteritis in two, atherosclerosis in three and non-specific chronic inflammation in four patients. Microbiological examination was negative in all but one patient who had *Salmonella* sp. cultured. Outcome was generally favourable, but one patient died from massive hemispheric infarction. There were no other new neurological deficits.

Conclusion: Carotid aneurysms pose a considerable surgical challenge but are amenable to operative intervention with good result. Ligation appears to be well tolerated in this group of predominantly non-atherosclerotic aneurysms.

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Introduction

The extracranial carotid artery is infrequently involved by aneurysms; few sizeable series have been reported. Catastrophic complications may result from untreated aneurysms, or may follow therapeutic intervention, making the management of such cases complex and challenging. Carotid aneurysms are not uncommon in a developing community such as South Africa[1]. This report reviews a recent experience in managing carotid aneurysms.

Patients and methods

The Metropolitan Vascular Service of the Department of Surgery, University of Natal offers a tertiary referral service at one academic and one secondary hospital in Durban, and drains a catchment area with an estimated population of 9–10 million people. The service undertakes all elective, and most emergency, cervical carotid surgery. All patients treated are entered into a computerized database. For the purpose of this study, patients with a carotid aneurysm seen between 1990 and 1998 were identified and clinical case records were reviewed. Thirty-nine patients were identified, ten of whom had a post-traumatic carotid false aneurysm. The remaining 29 patients, who had a total of 32 spontaneous aneurysms, form the basis of this report. No case of pseudoaneurysm following carotid endarterectomy was seen in this interval.

Results

All 29 patients were black South Africans. There were 24 men. The median age at presentation was 35 (range 13–62) years. Sixteen aneurysms were right sided and 16 left sided. Seven aneurysms were sited in the internal carotid artery (ICA); the remaining 25 involved the common carotid artery (CCA). Twelve of these were located at the carotid bifurcation. The external carotid artery was not involved in any patient. Clinical presentation was most frequently with a neck mass ($n = 23$) with compressive symptoms. One patient had an ipsilateral transient ischaemic attack and three presented with aneurysm rupture. Four patients were asymptomatic.

All the symptomatic carotid aneurysms were palpable with an audible bruit. One patient had a transient contralateral hemiparesis; there were no fixed central neurological deficits. Seven patients had a lower cranial nerve deficit (XII, five; X, four; cervicofacial branch of VII, one). Four patients had inspiratory stridor and four others admitted to a recent voice change. Indirect laryngoscopy was performed selectively; it showed ipsilateral vocal cord palsy in four, was normal in two, and inconclusive in the remaining two, in whom the vocal cords were obscured by bulging of the aneurysm into the pharynx. Three had clinical features of advanced human immunodeficiency virus (HIV) infection. One patient had established cardiac failure secondary to long-standing rheumatic valvular heart disease.

The results of serological testing for causes of aneurysms seen in this population are shown in *Table 1*. The diagnosis of carotid aneurysm was confirmed with duplex imaging. In addition, intra-arterial angiography was performed in all patients, with the exception of those presenting with haemorrhage or airway compromise from acute rupture.

Management

Five patients were treated conservatively; two refused surgery, and the patient with valvular heart disease and cardiac failure was considered unfit for an anaesthetic suitable for resection of a proximal left CCA aneurysm. The remaining two patients had acquired immune deficiency syndrome; one died from *Klebsiella* pneumonia 8 days after admission and the other had a symptomatic right subclavian aneurysm resected but would not consent to surgery for an asymptomatic left CCA aneurysm.

The remaining 24 patients (one with bilateral aneurysms; *Fig. 1*) were treated surgically, resulting in a total of 25 operations. Emergency surgery was required in four patients, one whose aneurysm ruptured in hospital the day before scheduled elective surgery, one in whom an aneurysm was aspirated at a peripheral hospital and who was referred 3 days later with rapid enlargement and airway compromise, and in two others who presented with acute airway compromise from a spontaneous contained rupture.

Table 1 Investigation of patients with carotid artery aneurysms ($n = 27$). Screening for atypical aneurysms commenced in 1994

	Positive	Negative
Syphilis serology	3	23
Widal serology for typhoid	1	21
HIV serology*	8	4
Mantoux test for tuberculosis	5	21

*Human immunodeficiency virus (HIV)

When pyogenic infection was suspected, carotid ligation was undertaken. This was done in four patients, two of whom had frank purulent sepsis and one with pyrexia and local induration. The last patient had local wound induration and a very friable ICA that would not hold sutures. Three patients had a spontaneous false aneurysm from a defect at the carotid bifurcation and were treated with patch closure of the debrided defect, using a Dacron (Du Pont, Wilmington, Delaware, USA) patch in two and a saphenous vein patch in one.

Interposition grafting was undertaken in the remaining 18 aneurysms. All anastomoses were end to end to the CCA; the distal anastomosis was to the CCA in seven and the ICA in 11 patients. The external carotid artery was ligated in ten patients in whom the graft was taken to the ICA, and was found to be occluded in one. Saphenous vein harvested from the groin was used for three grafts, expanded polytetrafluoroethylene (ePTFE) (Goretex; W.L. Gore, Flagstaff, Arizona, USA) for eight and Dacron for seven. All grafts were routed anatomically. A Pruitt–Inahara shunt was used to establish intraluminal control of the distal ICA in one patient with an aneurysm extending to the base of the skull which precluded dissection and circumferential control of the vessel (*Fig. 2*). In the remaining patients there was a mean stump pressure exceeding 50 mmHg and vigorous ICA backbleeding, so a carotid shunt was not used.

Wounds were routinely closed over suction drains, which were removed on the first day after operation. Antibiotic prophylaxis comprised ceftriaxone and cloxacillin, which was started at induction of anaesthesia and continued for 24 h, unless further antibiotic therapy was indicated by a

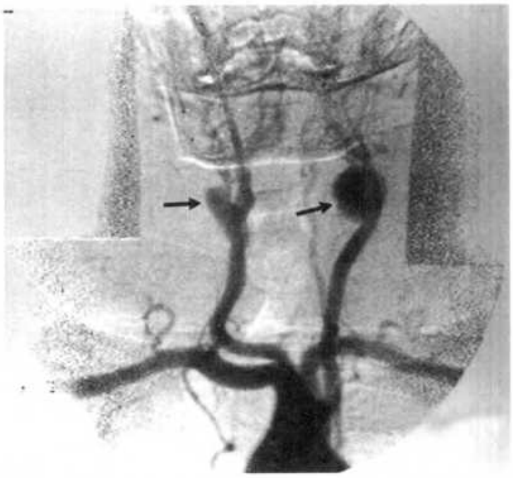

Fig. 1 Digital subtraction angiogram showing bilateral carotid bifurcation aneurysms (arrows), secondary to tuberculosis. Staged aneurysm resection and reconstruction using expanded polytetrafluoroethylene grafts was successful

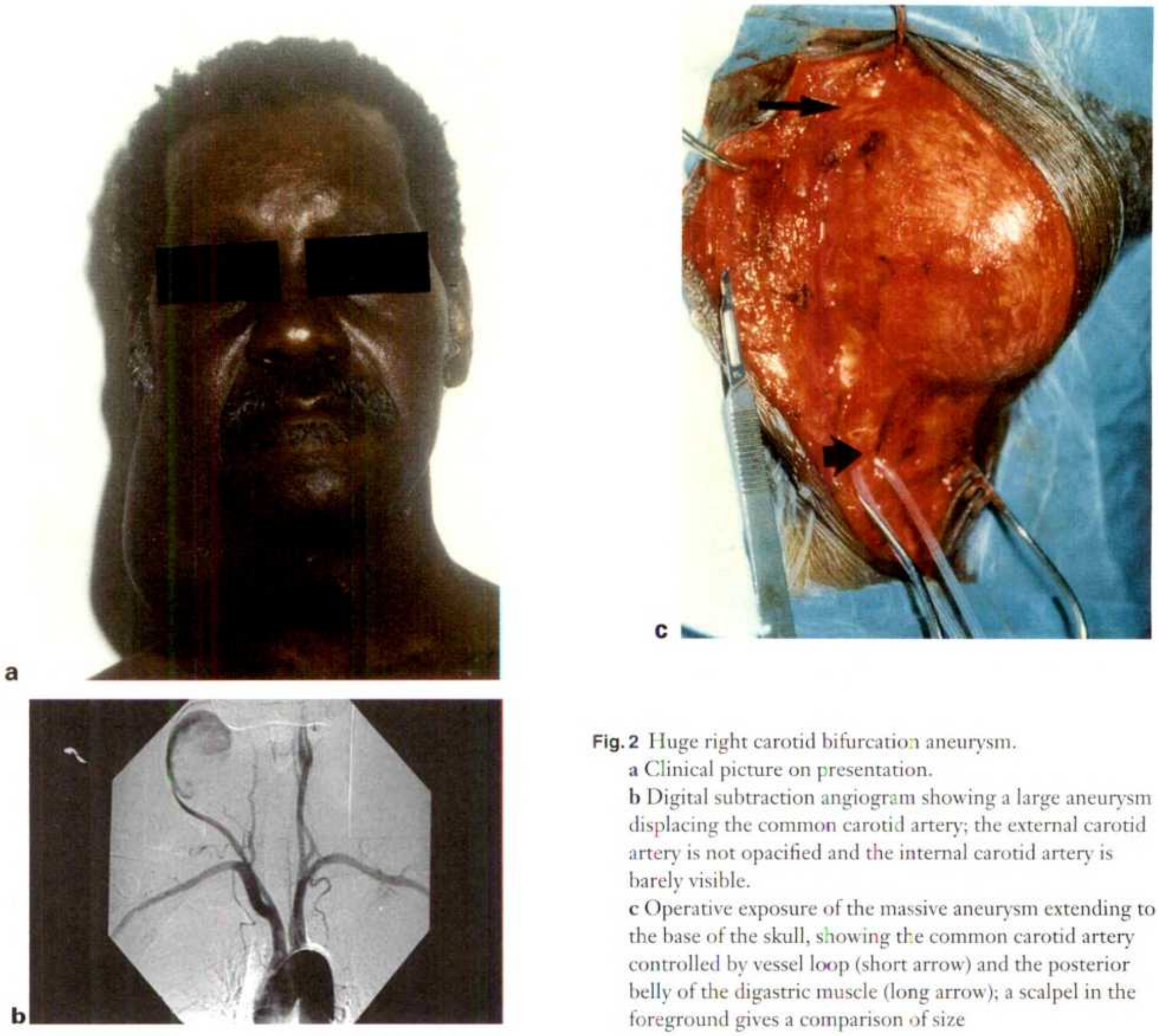

Fig. 2 Huge right carotid bifurcation aneurysm.
a Clinical picture on presentation.
b Digital subtraction angiogram showing a large aneurysm displacing the common carotid artery; the external carotid artery is not opacified and the internal carotid artery is barely visible.
c Operative exposure of the massive aneurysm extending to the base of the skull, showing the common carotid artery controlled by vessel loop (short arrow) and the posterior belly of the digastric muscle (long arrow); a scalpel in the foreground gives a comparison of size

positive bacterial culture. Additional antituberculous drug therapy was given after 12 operations (nine patients).

Aneurysm wall and the edges of false aneurysm defects were submitted for histological examination. Aneurysms were predominantly caused by tuberculosis or HIV (*Table 2*). Clot was routinely Gram stained and cultured; *Salmonella* sp. was isolated from one only.

Table 2 Histological features in 25 carotid aneurysms treated surgically

Tuberculosis	10
Non-specific inflammation	4
HIV*	4
Atherosclerosis	3
Syphilis	2
Takayasu's arteritis	2
Mycotic (*Salmonella*)*	1

**Salmonella* was isolated from a patient who also tested positive for human immunodeficiency virus (HIV) with coexisting histological features

Outcome

There was one perioperative death. A 19-year-old woman who had elective resection of a true aneurysm of the left ICA (histology demonstrated Takayasu's arteritis), and ePTFE interposition grafting from the CCA to the ICA, suffered an intraoperative hemispheric infarction. Intraoperative shunting was not performed, on the basis of a mean stump pressure of 59 mmHg. In the remainder, no other perioperative morbidity was noted; in particular, there were no other new postoperative cranial nerve or central neurological deficits. The patient who presented with a transient ischaemic attack had complete resolution of symptoms.

Follow-up data were available for 16 of the patients treated surgically with a median duration of 12 (range 1–60) months. One patient, who initially had a symptomatic CCA aneurysm (Takayasu's arteritis) repaired successfully, died 5 years later from rupture of an aortic arch aneurysm that had been deemed non-reconstructable at the original assessment. All other patients were well, with no neurological or graft-related complications. One patient who had been treated conservatively was seen 8 months later; there had been no complications from the aneurysm, which had not increased in size.

Discussion

Spontaneous aneurysms of the carotid artery are rarely encountered. Sir Astley Cooper performed the first ligation of a carotid aneurysm in 1805; the patient developed a hemiplegia and died. The first successful reconstruction for a carotid aneurysm was attributed to von Haberer in 1914[2]. While little is known abut the natural history of these lesions, there is consensus that they carry a poor prognosis if untreated[3]. Carotid aneurysms have been associated with a neurological deficit in as many as 96 per cent of cases in some series[4].

In South Africa, atherosclerotic involvement of the carotid arteries of black patients is infrequent, and infection and arteritis predominate as the causes. Causes of 12 carotid aneurysms previously encountered by the authors' service in a 10-year interval included atherosclerosis (four), Takayasu's arteritis (four), tuberculosis (one), syphilis (one), intimomedial mucoid degeneration (one) and mycosis (one)[1]. Because of the preponderance of arteritis and the low incidence of atherosclerosis, both the current and the previous series differ from other reports in that the mean age of the patients is considerably lower.

The rapid progression of the HIV epidemic in subSaharan Africa has had a major impact on all forms of medicine and vascular surgery is not exempt. In a previous publication it was noted that HIV aneurysms affected young patients and tended to involve multiple arteries at atypical sites[5]. A predilection for the carotid artery was noted in this cohort, the reasons for which were uncertain. Histological features have been described in detail[6].

All patients in the present series had an easily palpable cervical mass, even when the aneurysm was confined to the ICA, owing to the large size of most aneurysms at presentation. This study found a higher than expected incidence of bilateral aneurysms (three of 29 patients), compared with Schechter's review in which 33 bilateral aneurysms were noted in 820 patients[7]. Few asymptomatic carotid aneurysms are described in the literature, and their natural history is unknown. Three asymptomatic aneurysms in this cohort were detected by clinical examination and radiological imaging of patients with HIV who presented with symptomatic extracarotid aneurysms; the fourth was found incidentally in a patient with malignant hypertension.

One patient in the current series experienced transient ischaemic attacks, presumably from thromboembolism from the aneurysm sac. When not due to embolism, central neurological deficits may result from carotid thrombosis or compression by the aneurysm[8]. Deficits related to the seventh, tenth and 12th cranial nerves were seen in nine patients in this series[15]. Involvement of the fifth to 12th cranial nerves has been reported[9] and Horner's syndrome may result from the cervical sympathetic chain being affected. Rupture or bleeding from carotid aneurysms is rare. Bleeding after ill advised puncture of an aneurysm thought to be an abscess, as occurred in one patient, has also been reported previously[10].

Most extracranial carotid aneurysms are best managed surgically. Aneurysm resection and restoration of the cerebral circulation has had favourable results in most recent reports. Direct arterial repair by lateral suture for a small saccular aneurysm, transposition of external carotid artery to ICA, or end-to-end anastomosis have been described. None of these was possible in any of the patients treated by the authors. Saphenous vein is the graft of choice for carotid reconstruction, but size mismatch precluded its use in most cases, and made the use of prosthetic graft necessary. Spiral and panelled vein grafts could be used when the small calibre of the saphenous vein precludes simple interposition, but the time taken for their construction would prolong carotid occlusion time. Vein is preferred for arterial reconstruction following excision of a tuberculous aneurysm, as it can resist recurrent infection, when combined with a full course of antituberculous therapy[11].

Takayasu's disease is encountered relatively frequently in black African patients and in those of Indian extraction. The prevailing attitude towards vascular reconstruction appears to be pessimistic. The authors have adopted an aggressive approach and have achieved low mortality rates for surgery involving the aortic arch or its branches[12].

The management of a mycotic carotid aneurysm presents a major therapeutic dilemma. No practical route for extra-anatomic placement of grafts exists. Prosthetic grafts are contraindicated. Early reports advocated carotid ligation, as performed successfully by Ledgerwood and Lucas[13] in three patients. Monson and Alexander[14] first successfully used a saphenous vein graft to bypass a mycotic carotid aneurysm. Other reports of successful vein grafts have been published[15] but the recent literature still contains reports that ligation is the preferred option[16]. Howell *et al.*[16] concluded that the majority of grafts or arterial repairs fail if carried out in an infected field. The authors practised a policy of ligation. The lack of neurological sequelae from the four carotid ligations in this series is thought to be due partly to the underlying pathology being non-atherosclerotic, but also to the young age of the patients. Sparing of the intracranial and remaining extracranial vessels from atherosclerotic occlusive disease may result in less alteration to cerebral perfusion than might be expected in older patients with atherosclerosis. While no imaging of the intracranial circulation was performed, it is assumed that the patients treated by carotid ligation had adequate collateral perfusion via the Circle of Willis.

Recent publications have advocated the use of endovascular techniques to treat carotid aneurysms, with case reports of success with both covered[17] and bare[18] stents. The plethora of reports[19] citing complications from endovascular treatment of carotid stenosis raises concern. Surgeons are familiar with the often unstable thrombus within an aneurysm sac, and any endovascular procedure carries the risk of inducing distal embolization. The role of endovascular therapy in all forms of carotid disease is yet to be defined, but would appear most suitable for surgically inaccessible aneurysms.

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Original article

Influence of gender on outcome from ruptured abdominal aortic aneurysm

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Background: The aim of the present study was to compare outcomes following ruptured abdominal aortic aneurysm (AAA) in men and women.
Methods: Overall mortality from ruptured AAA was compared in men and women using the Western Australia Health Services Research Database. The linked chains of de-identified hospital morbidity and death records were selected using the ICD-9-CM (International Classification of Diseases - Clinical Modification) diagnostic and procedure codes pertaining to AAA. Cases were divided into three groups for analysis: patients who died without admission to hospital, those admitted to hospital with a ruptured AAA but who did not undergo operation, and patients who underwent operation for ruptured AAA.
Results: Ruptured AAA occurred in 648 men and 225 women over the age of 55 years during the decade 1985–1994. Only 50 per cent of women, compared with 59 per cent of men, were admitted to hospital. Of those admitted to hospital only 37 per cent of women underwent operation, compared with 63 per cent of men. The overall mortality rate from ruptured AAA was 90 per cent in women and 76 per cent in men ($\chi^2 = 50{\cdot}34$, 1 d.f., $P < 0{\cdot}0001$). Although women were, on average, 6 years older than men, this unfavourable pattern occurred across all age groups.
Conclusion: Women with a ruptured AAA are more likely to die than men. More research is required to identify the causes of this sex difference.

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Introduction

Although abdominal aortic aneurysms (AAAs) are less common in women than in men, there is increasing evidence that short- and long-term outcomes following both elective and emergency operation for AAA are poorer in women. Women have a greater risk of perioperative death following surgery for intact or ruptured AAA[1]. The 5-year relative survival rate after both elective and emergency surgery is also lower in women[2]. The aim of the present study was to compare outcomes following ruptured AAA in men and women. In addition to patients admitted to hospital with ruptured AAA, those who died before admission were also included as these patients comprise over 40 per cent of deaths from ruptured AAA[3].

Patients and methods

The Western Australia Health Services Research Linked Database[4] was used to link hospital morbidity and mortality records of all patients over the age of 55 years with a diagnosis of ruptured AAA during the interval 1985–1994. Cases were identified using the ICD-9-CM (International Classification of Diseases - Clinical Modification) diagnosis (441.30)[5] and procedure codes (before 1988, 58.53; from 1988 onwards, 38.44)[6,7], and were divided into three groups for analysis: patients who died without admission to hospital, those admitted to hospital with a ruptured AAA but who did not undergo operation, and those who underwent surgery for a ruptured AAA[3]. Data concerning all patients who died from AAA without being admitted to hospital for the study interval 1985–1994 were obtained from the Western Australia Death Register by means of the ICD-9 death code 4413 used by the Australian Bureau of Statistics. The de-identified file drawn from the Linked Database was current on 20 November 1996.

The differences between the proportions of men and women who died in the various categories were assessed with the χ^2 test; $P < 0{\cdot}05$ was considered statistically

Table 1 Number and ages of men and women presenting with a ruptured abdominal aortic aneurysm

	Women		Men			
	n	Mean(s.d.) (range) age (years)	*n*	Mean(s.d.) (range) age (years)	*t*	*P*
No admission	113	81·6(8·2) (64–97)	266	75·5(8·3) (56–94)	6·57	<0·0001
Admission, no operation	71	81·1(8·8) (60–100)	140	75·9(7·9) (58–92)	4·35	<0·0001
Operation	41	74·8(6·7) (55–92)	242	71·9(7·3) (55–90)	2·38	0·018
Total	225	80·2(8·5) (55–97)	648	74·2(8·1) (55–94)	9·45	<0·0001

significant. Differences in mean(s.d.) age between men and women for the three groups were determined with the unpaired *t* test.

Patients under the age of 55 years were excluded from the original masterfile as initial validation indicated that a high proportion were atypical[3]. There were eight such patients: one man who was not admitted to hospital, two men and one woman who were admitted but did not undergo operation, and three men and one woman who underwent operation. Exclusion of these patients did not change the clinical or statistical conclusions.

Results

Between 1985 and 1994, 1192 patients (177 women) underwent operation for an intact AAA; a detailed analysis of these operations has been reported previously[2,3]. During the same decade, rupture of an AAA occurred in 873 patients. The number and ages of patients in each category are summarized in *Table 1*. Women comprised 26 per cent (225 of 873) of all patients with a ruptured AAA. The proportion of women increased with age: 14 per cent (30 of 217) of 60–69 year olds, 20 per cent (70 of 348) of 70–79 year olds and 42 per cent (124 of 293) of those over 80 years of age.

The age-specific proportions of men and women in the three groups are given in *Tables 2–4*. Only 50 per cent (112 of 225) of women, compared with 59 per cent (382 of 648) of men with a ruptured AAA were admitted to hospital ($\chi^2 = 5{\cdot}35$, 1 d.f., $P = 0{\cdot}02$) (*Tables 2* and *3*). Of those admitted to hospital, only 37 per cent (41 of 112) of women underwent operation, compared with 63 per cent (242 of 382) of men ($\chi^2 = 8{\cdot}71$, 1 d.f., $P = 0{\cdot}003$) (*Tables 3* and *4*). As reported previously[2], the 30-day case fatality rate in women undergoing surgery for ruptured AAA was 44 per cent (18 of 41) compared with 35 per cent (84 of 242) in men ($\chi^2 = 5{\cdot}35$, 1 d.f., $P = 0{\cdot}02$) (*Table 4*). Thus, the overall mortality rate from ruptured AAA was 90 per cent (203 of 225) in women and 76 per cent (490 of 648) in men ($\chi^2 = 50{\cdot}34$, 1 d.f., $P < 0{\cdot}0001$).

Table 2 Number of men and women with ruptured abdominal aortic aneurysm and number who died before admission

	Men		Women	
Age group (years)	Total no. of patients	Died before admission	Total no of patients	Died before admission
55–59	14	6 (43)	1	0
60–69	187	70 (37)	30	12 (40)
70–79	278	109 (39)	70	33 (47)
≥80	169	81 (43)	124	68 (55)
Total*	648	266 (41)	225	113 (50)

Values in parentheses are percentages *$\chi^2 = 5{\cdot}35$, 1 d.f., $P = 0{\cdot}02$

Table 3 Number of men and women with ruptured abdominal aortic aneurysm admitted to hospital and number who died before undergoing surgical repair

	Men		Women	
Age group (years)	No. admitted	Died without operation	No. admitted	Died without operation
55–59	8	1 (12)	1	0
60–69	117	29 (25)	18	9 (50)
70–79	169	62 (37)	37	18 (49)
≥80	88	48 (55)	56	44 (79)
Total*	382	140 (37)	112	71 (63)

Values in parentheses are percentages. *$\chi^2 = 8{\cdot}71$, 1 d.f., $P = 0{\cdot}003$

Table 4 Number of men and women with ruptured abdominal aortic aneurysm who underwent operation and number who died within 30 days of surgery

	Men		Women	
Age group (years)	No. operations	No. deaths	No. operations	No. deaths
55–59	7	0	1	0
60–69	88	30 (34)	9	6 (67)
70–79	107	35 (33)	19	8 (42)
≥80	40	19 (48)	12	4 (33)
Total*	242	84 (35)	41	18 (44)

Values in parentheses are percentages. *$\chi^2 = 5{\cdot}35$, 1 d.f., $P = 0{\cdot}02$

Discussion

The present data confirm that, although ruptured AAA is more common in men, the female to male ratio increases with age. On average, women are about 6 years older than men when they present with a ruptured AAA (*Table 1*). Women with a ruptured AAA are much more likely to die than men. Initial inspection of the data suggests that the most likely explanation for the poor outcome in women is their greater age. However, the present study reveals that the likelihood of a man being admitted with a ruptured AAA and, if admitted, undergoing operation was greater in all age groups. As *Table 4* shows (albeit with small numbers), even for patients undergoing operation, women of all ages were more likely to die than men. A similar pattern exists when 5-year age-specific proportions are examined, although the numbers in some groups were too small to allow meaningful comparison (particularly for the 55–59 year olds). This study confirms a report from North America, which found that after admission to hospital men were 1·4 times more likely to have a ruptured AAA treated surgically[1]. In addition, the present data show that this unfavourable pattern also exists in women who never reach hospital.

At present it is possible only to speculate about reasons for the observed differences in outcome for men and women. These differences are similar to those seen in coronary heart disease where women have a worse outcome which is only partly explained by greater age[8]. As with coronary heart disease[9], women with an AAA may have worse risk factor profiles (other than age), resulting in greater co-morbidity. There is, for example, evidence from a population screening study that women with an AAA are more likely than men to be current smokers[10]. Increased co-morbidity could reduce the initial survival rate after the rupture of an AAA, influence decisions about operative intervention or increase postoperative case fatality. In the case of myocardial infarction, there is also evidence that women delay seeking medical attention and that this may contribute to their poorer outcome[11]. Another factor may be reduced awareness of AAA in women, resulting in diagnostic delays both before and after hospital admission. Although awareness about AAA is increasing, both ruptured and intact AAAs are regularly missed by clinicians at all levels of seniority[12].

Women are known to have smaller aortas than men[13] yet, in general, similar aortic diameters (> 5 cm in Western Australia) are used to define thresholds for diagnosis and elective surgery. This may underestimate the risk of aneurysm rupture in women and thereby delay intervention. Recent evidence comes from the UK Small Aneurysm Trial where the rate of rupture in women was three times that of men[14]. Furthermore the mean diameter at rupture was 5 cm in women and 6 cm in men. The problem of definition of AAA based on diameter alone for women remains unresolved[1]. The prevalence of AAA in women is currently considered too low for their inclusion in any of the various randomized controlled trials of ultrasonographic screening for AAA. This prevalence is, however, based on definitions used for men and may be an underestimate. While the ratio for the incidence of rupture between men and women was about 3 : 1 in the present study, the ratio of men to women undergoing elective operation for AAA during the same period[2] was almost 6 : 1. Similarly, a population-based screening study[15] found the prevalence ratio of men to women aged 65–80 years with an AAA was also almost 6 : 1. In other words, a disproportionate number of women present with a ruptured AAA rather than undergoing elective repair. While it is conceded that these women were, on average, 6 years older than the men with a ruptured AAA (*Table 1*), they are still dying from a condition that could have been detected and treated. Allowing for the greater life expectancy of women at all ages, there appears to be a need for greater attention to aneurysm disease in women.

More data are required on the incidence and natural history of AAA in women before any change to the criteria for intervention can be proposed, for example reducing the aortic diameter at which intervention is recommended to 5 cm. Meanwhile an increased awareness of the possibility of AAA may improve the outcome for women.

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Original article

Quantifying the risks of hypertension, age, sex and smoking in patients with abdominal aortic aneurysm

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Background: The prevalence of abdominal aortic aneurysm (AAA) in a community-based sample of men and women aged 65–79 years was correlated with known risk factors. In addition, the effect of high blood pressure and the use of antihypertensive medication on growth of AAAs were studied.

Methods: Aortic diameter was assessed by ultrasonography and data on risk factors were collected by self-administered questionnaire for 5356 men and women as part of a randomized controlled trial.

Results: Current hypertension increased the risk of having an aortic aneurysm by 30–40 per cent while use of antihypertensive medication increased the risk by 70–80 per cent, adjusting for current blood pressure. There was no clear relationship between hypertension and growth rates of existing aneurysms in this study, although these results were largely from data on small aneurysms. Men were nearly six times more likely to develop an AAA than women; the risk increased by 40 per cent every 5 years after the age of 65 years. Smoking was an independent risk factor for AAA, with level of exposure being more significant than duration.

Conclusion: Male sex, smoking and hypertension are strong risk factors for the development of AAA. In this study hypertension did not significantly increase the growth rate of existing aneurysms. Smoking remains the most important avoidable risk factor for AAA. The analyses presented here suggest that selection for screening, other than by age and sex, is not worthwhile.

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Introduction

Ruptured abdominal aortic aneurysm (AAA) causes 2·10 per cent of all deaths in men and 0·75 per cent of all deaths in women over the age of 65 years in England and Wales[1]. The incidence of asymptomatic AAA increases with age from 0·08 per cent of the male population at age 50 years to 0·67 per cent at age 65 years. Thereafter the incidence falls[2]. Recent attention has focused on secondary prevention of AAA, with a multicentre randomized trial underway to assess the benefits of screening by ultrasonography. Identification and quantification of avoidable risk factors might also help reduce the incidence of AAA.

Hypertension is a well documented risk factor for AAA[3–6]; it has been implicated in the pathogenesis, growth rate and risk of rupture of AAA[7]. Other risk factors commonly associated with AAA are male sex[1,8,9], age[1,3], smoking[10–12], vascular disease[13,14] and family history[15–17].

This was an investigation of the prevalence of AAA among patients with hypertension and those taking antihypertensive medication (normotensives and current hypertensives), relative to normotensive untreated subjects, in a community-based sample of men and women aged 65–79 years. The effect of hypertension on the growth rate of existing AAAs was also studied, and the risks associated with age, sex and smoking were quantified.

Patients and methods

The data used in these analyses were from a randomized controlled trial carried out in Chichester between 1988 and 1995, in which over 5000 men and women were screened for AAA. The methods and 5-year results of this study were published in 1995[8]. Anteroposterior measurements of aortic diameter were used; the maximum of the anteroposterior and transverse measurements was used as the defining diameter in the primary analysis and an aneurysm was defined as an aortic diameter of 30 mm or more. Aortic diameter was measured using a Pie Data SC480 (Pie Data UK, Crawley, UK) portable ultrasound machine. Blood pressure (BP) was recorded using a Critikon Dinamap 1846SX machine (Johnson and Johnson, Bracknell, UK). Population characteristics including information on demographics, medical and family history, smoking, occupation and medication were collected using a self-administered questionnaire, which was completed by the subject before attending the screening clinic. Data were available for 3035 women and 2321 men. Usually only the median systolic (of three) and the associated diastolic BP were recorded for each subject, but in a subsample of 1884 men (81 per cent), three BP readings were available. When analysing this subset, to adjust for the fact that a single measure of a continuous variable (in this case BP) is not a good estimate of usual level, adjustment for this regression dilution bias was made using the method described by MacMahon *et al.*[18].

To investigate the effects of BP, antihypertensive medication, age, sex and smoking on aortic diameter, odds ratios were calculated by fitting logistic regression models to the variables of interest. To adjust for possible confounding, models included age, sex and smoking status. The odds ratios calculated in these analyses represent an estimate of the relative risk.

The effects of hypertension and use of antihypertensive medication on the growth of AAAs were also investigated, using a longitudinal data set from the Chichester study; 504 patients identified as having an AAA were followed as part of the usual screening protocol.

Results

Patients with current hypertension

Table 1 shows the prevalence and risk estimates for having an AAA among individuals with hypertension defined in various different ways. In the first case, the diagnosis of hypertension was based on one BP measurement taken at the time of the initial ultrasonographic scan. Raised diastolic BP increased the risk of having an AAA by between 30 and 40 per cent, depending on the definition of hypertension. The risk posed by diastolic BP increased linearly and the crude linear trend was significant ($P = 0{\cdot}005$). Raised systolic BP did not significantly increase the risk of having an AAA and there was no evidence of a trend.

Patients taking antihypertensive medication

Table 2 shows crude and adjusted odds ratios for having an AAA for patients currently or previously receiving anti-

Table 1 Prevalence of abdominal aortic aneurysm and crude and adjusted risk estimates among patients with hypertension

	No.	Prevalence (%)	OR$_1$	*P*	OR$_2$	*P*
Diastolic BP (mmHg)*						
<90	4014	3·3	1·0		1·0	
≥90	1028	4·8	1·5 (1·1–2·1)	0·024	1·4 (1·0–2·0)	0·045
Diastolic BP (mmHg)†						
<100	4711	3·5	1·0		1·0	
≥100	331	4·5	1·3 (0·8–2·2)	0·342	1·3 (0·8–2·2)	0·421
Diastolic BP (mmHg)				0·005‡		0·008‡
<70	1157	2·8	1·0		1·0	
70–79	1510	3·0	1·1 (0·7–1·7)		1·0 (0·7–1·7)	
80–89	1347	4·1	1·5 (1·0–2·3)		1·5 (1·0–2·2)	
90–99	697	4·9	1·8 (1·1–2·9)		1·8 (1·0–2·9)	
≥100	331	4·5	1·7 (0·9–3·1)		1·6 (0·9–3·0)	
Systolic BP (mmHg)*						
<160	2694	3·7	1·0		1·0	
≥160	2348	3·4	0·9 (0·7–1·2)	0·515	0·9 (0·7–1·2)	0·438
Systolic BP (mmHg)†						
<200†	4586	3·6	1·0		1·0	
≥200	456	3·9	1·1 (0·7–1·8)	0·667	1·1 (0·7–1·8)	0·755
Systolic BP (mmHg)				0·880‡		0·778‡
<160	2694	3·7	1·0		1·0	
160–179	1197	3·2	0·8 (0·6–1·2)		0·8 (0·5–1·2)	
180–199	695	3·5	0·9 (0·6–1·4)		0·9 (0·5–1·4)	
≥200	456	3·9	1·1 (0·6–1·8)		1·1 (0·5–1·7)	

Values in parentheses are 95 per cent confidence intervals. *World Health Organization definition of hypertension. diastolic blood pressure (BP) > 90 mmHg, systolic BP > 160 mmHg; †common clinical definition of hypertension diastolic BP > 100 mmHg, systolic BP > 200 mmHg. OR$_1$, crude odds ratio; OR$_2$, odds ratio adjusted for age, sex and smoking. ‡Single *P* value for trend

Table 2 Prevalence of abdominal aortic aneurysm and crude and adjusted risk estimates for age, sex, smoking and antihypertensive medication

	No	Prevalence (%)	OR_1	*P*	OR_2	*P*
Sex						
F	2832	1·1	1·0		1·0	
M	2203	6·8	6·6 (4·5–9·8)	0·000	5·6 (3·7–8·4)	0·000
Age (years)						
65–69	1905	2·7	1·0		1·0	
70–74	1636	3·9	1·4 (0·98–2·1)	0·062	1·4 (0·98–2·1)	0·058
75–79	1459	4·4	1·7 (1·1–2·4)	0·008	1·8 (1·2–2·7)	0·002
Smoking						
Never	1961	1·6	1·0		1·0	
Ever	3089	3·1	3·1 (2·1–4·5)	<0·001	1·8 (1·2–2·7)	0·004
Antihypertensives						
Never	3765	3·1	1·0		1·0	
Ever	1260	5·1	1·7 (1·2–2·3)	0·001	1·8 (1·3–2·5)	<0·001
Antihypertensives						
Not current	3789	3·1	1·0		1·0	
Current	1236	4·9	1·6 (1·2–2·2)	0·004	1·7 (1·3–2·4)	0·001

Values in parentheses are 95 per cent confidence intervals. OR_1, crude odds

hypertensive medication. Patients who had ever taken medication had an 80 per cent increased risk of having an AAA compared with subjects who had never had medication, after adjusting for age and sex. The odds ratio decreased to 1·7 (95 per cent confidence interval (c.i.) 1·3–2·4) when comparing 'not current' *versus* 'current' use. Adjusting for current BP made no difference to these odds ratios. This may imply that the use of medication, a proxy for long-term hypertension, irrespective of current BP, increased the risk of having an AAA. These results support the findings of Alcorn *et al.*[19], who also reported an increase in the prevalence of AAA among patients with treated hypertension.

Table 3 Growth rates of abdominal aortic aneurysms in subjects with hypertension and those on antihypertensive medication

	Increase per year (%)	*P*
Systolic BP (mmHg)		
<160	3·15 (1·96–4·34)	0·6
≥160	3·73 (2·02–5·44)	
Diastolic BP (mmHg)		
<90	3·35 (2·28–4·27)	0·7
≥90	3·90 (1·52–6·35)	
Antihypertensive drug use		
No/previous	3·01 (1·76–4·27)	0·08
Current	4·78 (3·27–6·21)	

Values in parentheses are 95 per cent confidence intervals. BP, blood pressure

Aneurysm growth rates and hypertension

There was no significant effect of hypertension on the growth rate of existing aneurysms. The difference in recent growth over 1 year was less than 1 per cent more in patients with an AAA and raised systolic or diastolic BP (*Table 3*). Growth rates of existing AAAs in the same population of patients with treated hypertension were also investigated. Although a proportionally larger increase in growth was observed, absolute growth rates were small both in those with and in those without a history of treatment for hypertension.

Three measures of blood pressure

Analysis of the subset of 1884 subjects who had a series of three BP measurements showed that only diastolic BP was a risk factor for AAA. MacMahon *et al.*[18] have shown that a single BP measurement is not a good representation of usual BP, suffering from over-dispersion due to within-person variability and measurement error. This can be corrected by repeated measurement within categories of the first measure. The range of a third measurement of BP was 81 per cent of the range of the first, conditional on the first. Using the first measure, a trend of increasing risk of 14 per cent per 10 mmHg (diastolic BP) was observed. The repeat measures suggested that the trend was 18 per cent per 10 mmHg; the first measure underestimated the risk posed by BP presented in *Table 1*, by 22 per cent.

Mean arterial pressure and pulse pressure

In the search for a mechanism whereby raised BP leads to an increased risk of AAA, the influence of mean arterial and

Table 4 Cumulative risk of abdominal aortic aneurysm per years of smoking and per cigarette per day

	OR_1	*P*	OR_2	*P*
For each cigarette smoked per day	1·06 (1·04–1·09)	<0·001	1·04 (1·01–1·05)	0·005
For each year of habit	1·04 (1·02–1·06)	<0·001	1·03 (1·01–1·05)	<0·001

Values in parentheses are 95 per cent confidence intervals. OR_1, crude odds ratio, OR_2, odds ratio adjusted for age and sex

Table 5 Prevalence of abdominal aortic aneurysm and crude and adjusted risk estimates for duration of smoking and level of exposure

	No.	Prevalence (%)	OR_1	*P*	OR_2	*P*
Smoking						
Never	1961	1·6	1·0		1·0	
Ever	3089	3·1	3·1 (2·1–4·5)	<0·001	1·8 (1·2–2·7)	0·004
Smoking						
Never	1961	1·6	1·0		1·0	
Ex	2285	4·2	2·6 (1·7–3·9)	<0·001	1·5 (1·0–2·3)	0·053
Current	804	6·8	4·4 (2·8–6·9)	<0·001	2·7 (1·7–4·4)	<0·001
No. of cigarettes (per day)						
Current smokers				<0·001*		<0·001*
0	1961	1·6	1·0		1·0	
1–9	87	1·1	0·7 (0·1–5·0)		0·7 (0·1–5·5)	
10–19	211	5·4	3·4 (1·7–6·8)		3·0 (1·5–6·0)	
20–24	192	7·2	4·7 (2·5–8·9)		2·9 (1·5–5·6)	
⩾25	95	15·2	10·8 (5·8–20·1)		5·5 (2·8–10·6)	
Ex-smokers				<0·001*		0·012*
0	1961	1·6	1·0		1·0	
1–9	420	2·4	1·5 (0·7–3·0)		1·4 (0·7–2·9)	
10–19	671	2·4	1·5 (0·8–2·7)		1·0 (0·5–1·8)	
20–24	541	5·0	3·2 (1·9–5·3)		1·8 (1·0–3·1)	
⩾25	373	6·2	4·0 (2·3–6·9)		1·9 (1·0–3·4)	
Duration of smoking (years)				<0·001*		<0·001*
0	1961	1·6	1·0		1·0	
1–9	165	1·8	1·1 (0·3–3·7)		0·9 (0·3–2·9)	
10–19	295	1·7	1·0 (0·4–2·7)		0·6 (0·2–1·6)	
20–29	433	2·3	1·4 (0·7–2·9)		0·9 (0·4–1·8)	
30–39	583	3·4	2·1 (1·2–3·8)		1·3 (0·7–2·4)	
⩾40	1485	7·1	4·6 (3·1–6·9)		2·5 (1·7–3·9)	

Values in parentheses are 95 per cent confidence intervals. OR_1, crude odds ratio, OR_2, odds ratio adjusted for age and sex. *Single *P* value for trend

pulse pressure was investigated. Pulse pressure was defined as systolic minus diastolic pressure. Mean arterial pressure was the average pressure during the cardiac cycle. Although integrating the area of the pressure curve during one cycle is the best method for calculating mean arterial pressure, an approximation was made by adding one-third of the pulse pressure to the diastolic measurement. No correlation between either measure and the presence of AAA was observed.

Variability of blood pressure

The possibility of variability in BP having an effect on the prevalence of AAA was investigated. The minimum of the series of either systolic or diastolic BP measurements was subtracted from the maximum observed, to assess the variability of BP during three subsequent readings. No statistically significant relationship was observed between variability and the presence of AAA. Using the definitions of hypertension seen in *Table 1*, and stratification of both systolic and diastolic BP, there was no increase in the prevalence of AAA among subjects with variable BP.

Age, sex and smoking

The prevalence of AAA is also shown in *Table 2* with crude and adjusted risk estimates by age, sex and smoking habit. The prevalence of AAA among men aged 65–79 years was 6·8 per cent, more than six times that observed in women. After adjusting for age and smoking, men in this population were 5·6 times more likely to have an AAA than women. The prevalence of AAA increased steadily with age, from 2·7 per cent at ages 65–69 years (men and women) to 4·4 per cent at 75–79 years. This significant linear trend was also seen when a logistic regression model was fitted, even after adjusting for sex ($P = 0{\cdot}004$). This result mirrors that published by Pleumeekers *et al.*[20], who observed that the prevalence of AAA was 5·9 (95 per cent c.i. 3·7–9·5) times higher in men than in women.

In this study, men and women self-reported the average number of cigarettes smoked daily and the age at which they first smoked. The level of cigarette consumption was a stronger risk indicator than duration of smoking habit (*Table 4*). Similarly the odds ratios for smoking, 'ever' *versus* 'never' and 'never' *versus* 'ex' and 'current', showed increasing risks of AAA with exposure and years of habit (*Table 5*). Subjects were divided into those who had never smoked, current and ex-smokers, the latter having stopped for a mean of 20·2 years. The benefits of stopping smoking were illustrated by the reduction in risk for ex-smokers compared with current smokers, and when examining the level of exposure. Risk estimates by number of cigarettes consumed were explored for ex-smokers and current smokers separately. There was a marked decrease in risk in all categories when ex-smokers were compared with current smokers, except in those smoking one to nine cigarettes per day. This did not reach statistical significance. Similar findings were published in 1991 by Bengtsson *et al.*[21]. The duration of smoking habit included both ex-smokers and current smokers. This cohort of men and women all started smoking at a similar age, so it was not possible to separate the length of exposure from the time since stopping smoking. Current smokers were therefore over-represented in the larger categories.

Discussion

The results presented in this paper suggest that there is an increase in the prevalence of AAA among patients aged over 65 years with current hypertension. This contradicts the findings of Collin *et al.*[22] who reported 'no significant differences between prevalence of hypertension in patients with aneurysmal disease and those without', but their observations were based on only 24 clinic-based subjects. The analysis presented here suggests that long-term hypertension, as indicated by the current or previous use of antihypertensive medication, irrespective of current BP, increases the likelihood of having an AAA by as much as 80 (95 per cent c.i. 1·3–2·5) per cent. The effect of current or long-term hypertension on the growth of an AAA was not significant, although results with respect to the latter were suggestive. These results were, however, based on the growth of comparatively small aneurysms. Aortic diameter measurement over time is also subject to investigation error, which has been estimated to be as much as ± 5 mm[23].

Hypertension may be a factor predisposing to AAA, or it may affect the growth rate or risk of rupture of an existing aneurysm. A distinction also needs to be made between current high BP at the time of investigation and long-term hypertension. Current use of antihypertensive medication may be a proxy measure for long-term hypertension.

Male sex is the greatest risk factor for AAA; men are 5·6 (95 per cent c.i. 3·7–8·4) times more likely than women to have an AAA after adjusting for age and smoking. The risk of having an AAA increases with age, with the 75–79-year-old population being nearly twice as likely to have an AAA than a group aged 65–69 years. While the prevalence of AAA increases with age, the incidence peaks at around age 65 years[2]. Although AAAs do develop after the age of 65 years, it has been suggested that rescreening of patients found to have a normal aortic diameter at first scan (aged 65 years) is subject to diminishing returns[24].

Evidence for the association between smoking and AAA was first provided by the Framingham Study in 1967[25]. Smoking is the largest avoidable risk factor for AAA; life-time male smokers are 2·5 (95 per cent c.i. 1·5–4·4) times more likely to develop an AAA than life-time male non-smokers. Ex-smokers have a slightly lower relative risk of 1·5 (95 per cent c.i. 0·9–4·4). Consideration of the number of cigarettes smoked and the length of smoking habit reveals increasing odds ratios for an AAA according to the number of cigarettes consumed daily and the duration of smoking. Only the larger categories for both variables reached statistical significance, but a trend was observed for both.

The most important risk factor for an AAA is male sex, followed by smoking and age; use of antihypertensive medication and diastolic BP are also implicated. If screening for AAA is adopted, these analyses do not support selection other than by age and sex. The proportion of aneurysms attributable to smoking (assuming a 40 per cent prevalence of smoking) is estimated to be 24 per cent. The proportion attributable to raised diastolic BP (above 90 mmHg) is estimated to be 8 per cent and that attributable to male sex is 70 per cent.

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Original article

Diaphragmatic dysfunction secondary to experimental lower torso ischaemia–reperfusion injury is attenuated by thermal preconditioning

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Background: Preconditioning describes the process whereby tissue exposure to a subcritical stress confers protection from subsequent injuries. This study assessed diaphragmatic muscle function after lower torso ischaemia–reperfusion (IR) and the role of thermal preconditioning in attenuation of this injury.

Methods: Sprague–Dawley rats were randomized into three groups (24 per group): a control group, an IR group that had aortic cross-clamping for 1 h followed by reperfusion, and a third group that received thermal preconditioning 18 h before IR. Diaphragmatic function was assessed at 24 h, 48 h and 7 days.

Results: IR resulted in significant diaphragmatic twitch and tetanic dysfunction compared with control muscle. Thermal preconditioning significantly attenuated this injury ($P < 0{\cdot}05$). Mean(s.e.m.) muscle twitch and tetanic forces in the IR group were 204·9(17·2) and 282·7(19·2) g respectively at 24 h. Corresponding twitch and tetanic forces in preconditioned muscle were 270·4(25·1) and 552·0(35·2) g.

Conclusion: This study demonstrated that systemic IR injury produced a respiratory muscle mechanical dysfunction that was attenuated by thermal preconditioning, at 24 h, 48 h and 7 days. Preconditioning may have a role in clinical practice, particularly before elective surgery.

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Introduction

Respiratory complications after surgery or major injury continue to constitute a significant component of postoperative morbidity and mortality rates. This is particularly so in relation to aortic surgery, with its associated lower torso ischaemia–reperfusion (IR) injury, after which up to 60 per cent of patients will develop respiratory complications. Studies have concentrated on inflammatory cell- and cytokine-mediated pulmonary parenchymal injury as an explanation for this injury[1,2]. The parenchymal element constitutes an injury to one component of the respiratory system, namely the gas exchange mechanism. Respiratory muscle dysfunction with impairment of the ventilatory mechanism may also contribute.

Exposure to sublethal noxious stimuli, such as hyperthermia or ischaemia, preconditions cells to resist a subsequent stress that would otherwise be lethal. Thermal preconditioning, whereby this effect is induced by a temperature increase, decreases neutrophil–endothelial adhesion and subsequent transmigration, thus preventing IR-induced tissue injury[3]. This protective effect appears to be mediated in part by expression of heat-shock proteins (HSPs), of which the 70-kDa HSP family is the most highly inducible[4]. The mechanism whereby HSPs exert their protective effects has been described as analogous to that of a molecular chaperone. They prevent premature protein folding and denaturation[5]. The HSP chaperone effect allows normal protein folding, assembly, disassembly and interactions to proceed in adverse cellular environmental circumstances. This activity is potentially of particular significance in allowing normal muscle contractile protein function to continue under stressful conditions.

Respiratory muscle dysfunction contributes to clinically relevant ventilatory pump failure in sepsis and endotoxaemia[6,7]. In addition, respiratory muscle dysfunction has been shown to contribute to death in patients with adult respiratory distress syndrome, causing difficulty in weaning from mechanical ventilation[2,8].

The aim of this study was to assess whether lower torso IR injury, secondary to temporary aortic cross-clamping, results in diaphragmatic dysfunction and, furthermore, whether thermal preconditioning could preserve muscle function.

Materials and methods

Animals and thermal preconditioning

All animal procedures were carried out in an approved animal research facility, under licence from the Department of Health, Republic of Ireland. Sprague–Dawley rats (300–350 g) were maintained on a diet of purified chow pellet and water. The rats were randomized into three groups: a control group subjected to laparotomy and sham IR, an IR group that had aortic cross-clamping for 1 h followed by reperfusion, and a group that received thermal preconditioning 18 h before IR. Animals were killed and studied at 24 h, 48 h and 7 days, with eight animals in each of the three groups, at each of the three time points.

Thermal preconditioning was induced by raising the core body temperature to 41 ± 0·5°C by partial immersion in a water bath (Grant Instruments, Shepreth, UK) for 15 min under anaesthesia with inhalational halothane (May and Baker, Dagenham, UK). The animal's temperature was gradually increased with continuous monitoring by rectal thermometer. Thermal preconditioning was performed 18 h before IR.

Rat systemic ischaemia–reperfusion injury model

The rats were anaesthetized with inhalational halothane and prepared for surgery. A midline laparotomy incision was made and the aorta dissected free below the origin of the renal arteries. A microvascular clamp was used to occlude the aorta for 1 h. After this time the clamp was removed and the lower torso was reperfused. The control group was subjected to the same procedure and dissection, but without aortic clamping. The abdominal wound was sutured with 4/0 nylon. Analgesia was administered as 0·1 ml buprenorphine 0·3 mg/ml intramuscularly. The rats were then returned to their cages with free access to food and water.

Muscle function studies

Muscle contractile function was assessed by direct stimulation of central strips of left hemidiaphragm[9–11]. The rat was anaesthetized with inhalational halothane. A left thoracoabdominal incision allowed access to the left hemidiaphragm. Two parallel vertical incisions, 3 mm apart, were made centrally in the left hemidiaphragm. The incisions ran anteroposteriorally and included the tendinous attachments of the diaphragm on to its origins. The isolated muscle strip and its attachments were then excised *en bloc*.

The fresh muscle sample had silk sutures secured to each end and was then suspended between platinum electrodes 1 cm apart in a twin-walled water-jacketed glass tissue chamber (Radnoti Glass Technology, Monrovia, California, USA). One end of the muscle was fixed and the other attached to an isometric force transducer with a tissue clip (Radnoti Glass Technology). The muscle was maintained in oxygenated Krebs physiological solution at pH 7·4 in the 37°C organ bath. Muscle length was adjusted to that at which twitch isometric force production was maximal at 20 V for 2 ms at 40 Hz (Pulse Generator Harvard Stimulator; Harvard Apparatus, Edinbridge, UK). Maximal twitch and tetanic muscle function in response to electrical stimulation was assessed. Results were expressed as mean(s.e.m.) grams of force per gram of muscle.

The data were collected and analysed using a commercially available computerized data acquisition program (MacLab AD Instruments, Hastings, UK) on line with a Macintosh Powerbook. Analysis of variance and the Scheffe *post hoc* test were used for statistical comparisons. $P < 0·05$ was considered significant.

Results

Heat shock protein expression

Expression of HSP in diaphragm muscle after thermal preconditioning was confirmed by the use of Western blotting techniques (*Fig. 1*).

Effect of ischaemia–reperfusion on diaphragmatic function (*Figs 2 and 3*)

The control group of animals had a mean twitch function of 367·4(21·7) g and tetanic function of 757·0(45·4) g. Animals subjected to lower torso IR had a significant deterioration in diaphragmatic contractile performance after 24 h compared with controls, which was significantly attenuated by thermal preconditioning. Forty-eight hours after IR there was ongoing statistically significant diaphragmatic muscle dysfunction in the IR group compared with control muscle, which again was attenuated by thermal preconditioning. Findings were similar after 7 days.

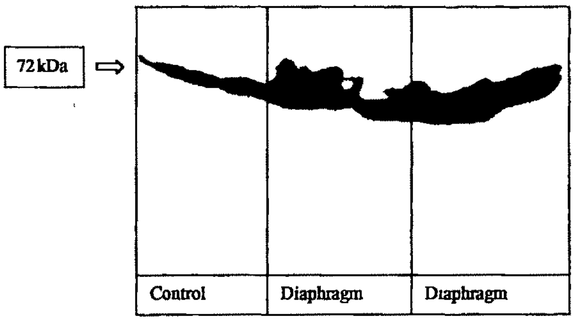

Fig. 1 Western blotting for heat shock protein 72 expression in diaphragm muscle 18 h after thermal preconditioning

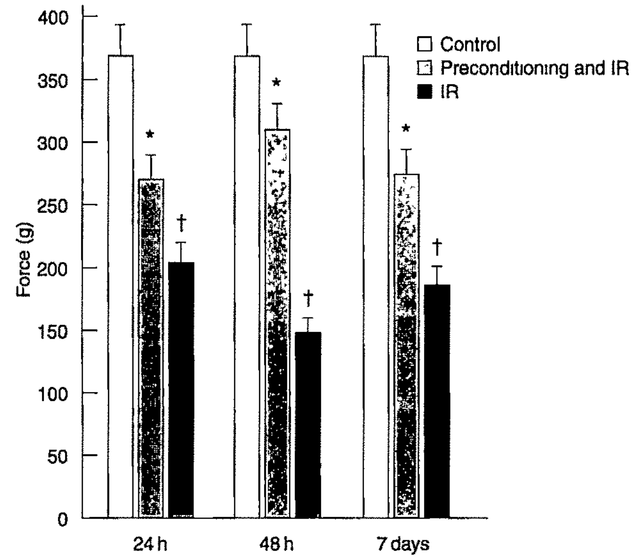

Fig. 2 Diaphragmatic twitch function after systemic ischaemia–reperfusion (IR) injury. Values are mean(s.e.m.). $^*P < 0.05$ *versus* IR; $^\dagger P < 0.05$ *versus* control (Scheffe *post hoc* test)

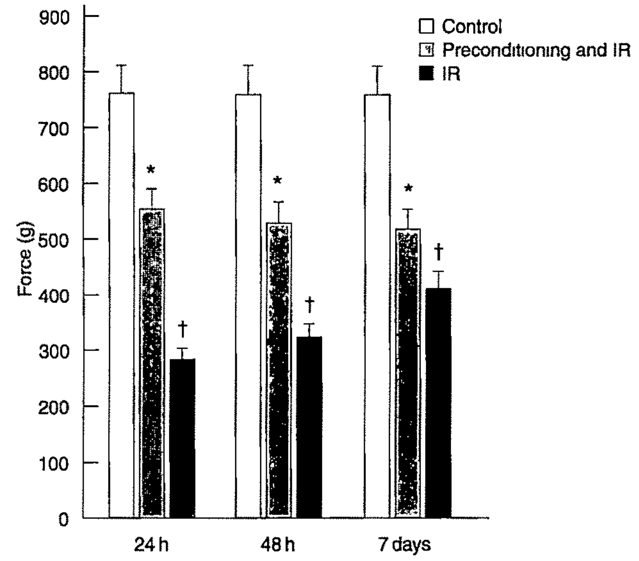

Fig. 3 Diaphragmatic tetanic function after systemic ischaemia–reperfusion (IR) injury. Values are mean(s.e.m.). $^*P < 0.05$ *versus* IR; $^\dagger P < 0.05$ *versus* control (Scheffe *post hoc* test)

Discussion

Respiratory failure is a frequent clinical finding in the course of sepsis, trauma or after major surgery. Pulmonary parenchymal injury has received much attention in this regard; however, more recently the concept of impaired respiratory muscle contractile performance aggravating this condition has evolved[2,6,7,11]. Conditions such as sepsis and endotoxaemia, which produce an analogous systemic inflammatory response syndrome (SIRS), induce similar diaphragmatic dysfunction[6,7]. Lower torso IR also causes SIRS[1]. This study demonstrated that lower torso IR also induces diaphragmatic dysfunction.

Muscle contractile function assessment using peak force contraction in response to electrical field stimulation is a well recognized and effective method of testing skeletal muscle function[9]. Direct tetanic stimulation permits simultaneous activation of all sarcomeres and therefore gives a valid estimate of the function of the contractile elements and the excitation–contraction coupling systems, independent of nerve function[10,12]. The diaphragm *in vivo* may display a postlaparotomy dysfunction that is due in part to neuronal inhibitory reflex activity[13]. The methodology used in this study has the advantage of eliminating this reflex inhibition as a component of observed muscle physiological performance. Studies using similar methodology have demonstrated diaphragmatic dysfunction after endotoxaemia[6].

Several underlying mechanisms may contribute to this respiratory muscle injury. These include neutrophil infiltration[1], and the action of proinflammatory cytokines[14,15], prostaglandins[16], reactive oxygen species and nitric oxide[17]. Previous studies have implicated oxygen free radical generation in the development of respiratory muscle dysfunction[1,13]. This is associated with increased electron spin resonance[18], lipid peroxidation, protein carbonyl formation and glutathione oxidation[19] in affected muscles. Oxygen free radicals interfere with function through cellular calcium overload, protein malfolding and denaturation causing diminished calcium affinity of the myofilamental proteins[20–22]. HSPs have a well described role in the protection of myocardial muscle proteins against the damaging effects of free radicals in reperfusion and ischaemic injury[23,24]. The mechanisms whereby thermal preconditioning confers protection may not be limited to the induction of HSPs, as the induction process of preconditioning has protective effects on endothelial function, neutrophil activation and neutrophil–endothelial interactions. Significantly, thermal preconditioning has direct effects on myocytes themselves, through chaperoning of actin and myosin protein interactions[3,5,24,25]. This allows the actin–myosin protein interactions that produce muscle contraction to proceed in a stressed situation. All of these protective mechanisms are potentially at play in IR injury. In addition to the intracellular protein effects on myocytes, thermal preconditioning protects endothelial cells of vessels supplying the muscle against polymorphonuclear cell-mediated damage, thus allowing maintenance of endothelial barrier function[25,26].

In a previous study, thermal preconditioning was used to protect skeletal muscle against morphological and biochemical change manifested as mitochondrial damage on electron microscopy, creatinine phosphokinase release and reduced adenosine 5′-triphosphate levels following ischaemic injury[27]. In contrast, the present study primarily assessed the consequences of IR-mediated injury on muscle electrophysiological function rather than morphological and biochemical criteria.

In conclusion, this study showed that systemic IR injury resulted in a functional diaphragmatic muscle injury. Thermal preconditioning significantly attenuated this injury. Preconditioning may have clinical application in attenuation of respiratory muscle injury and associated ventilatory pump dysfunction.

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Original article

Bladder and sexual dysfunction after mesorectal excision for rectal cancer

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Background: Urinary and sexual dysfunction are recognized complications of rectal excision for cancer. The aim of this study was to examine the frequency of such complications after mesorectal excision, shortly after this method was introduced.

Methods: Spontaneous flowmetry, residual volume of urine measurement and urodynamic examination, including cystometry and simultaneous detrusor pressure and urinary flow recording, was carried out before and 3 months after curative rectal excision. Urinary symptoms and sexual function were evaluated by means of questionnaires before and after operation. Each patient served as his or her own control.

Results: Forty-nine consecutive patients, 39 of whom had a total mesorectal excision (TME) and ten a partial mesorectal excision, were examined before surgery and 35 again after operation. In two patients, a weak detrusor was detected before operation. Two patients developed signs of bladder denervation after operation. Transitory moderate urinary incontinence appeared in four other women. Six of 24 men reported some reduction in erectile function and one became impotent. Two men reported retrograde ejaculation. All the complications were seen in the TME group.

Conclusion: Mesorectal excision for rectal cancer resulted in a low frequency of serious bladder and sexual dysfunction.

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Introduction

Urinary and sexual dysfunction are recognized complications of rectal resection for carcinoma. The main cause of dysfunction seems to be injury to the autonomic nerves in the pelvis and along the distal aorta. The incidence of genitourinary dysfunction depends on the type of operation performed, i.e. the plane of dissection, the degree of preservation of the autonomic nerves and the extent of pelvic dissection[1–11]. Dysfunction is more common after abdominoperineal resection (APR) than after low anterior resection (LAR)[12–14].

Total mesorectal excision (TME), according to the technique described by Heald[15–17], was introduced as the standard method for treatment of rectal cancer in the authors' departments in 1992. In this operation the autonomic nerves are carefully preserved and one would expect few genitourinary complications. The present study was performed to examine the frequency of bladder and sexual dysfunction that occurred after mesorectal excision in a consecutive series of patients.

As recognition of urinary and sexual dysfunction depends on the methods used for evaluation[18,19], urodynamic investigation, including simultaneous detrusor pressure and urinary flow measurements, was performed both before and after the operation. Each patient served as his or her own control. To date, few studies using these techniques have been published, and none has examined the outcome after mesorectal excision.

Patients and methods

Fifty-eight consecutive patients with rectal cancer located 15 cm or less from the anal verge were included from 1996 to 1998. All were scheduled for curative resection using the TME technique, and none had received preoperative radiotherapy. There were three postoperative deaths. Two patients who received postoperative radiotherapy were excluded. Among the remaining 53 patients, the initial urodynamic investigation was unsuccessful in two, and two other patients had uninhibited detrusor contractions. Thus, 49 patients remained in the study.

There were 22 women and 27 men with a median age of 63 (range 26–80) years. Tumour stage and type of operation are summarized in *Table 1*. The primary tumours were equally distributed in the lower, middle and upper rectum. In ten patients in whom the tumour was located in the upper rectum, partial mesorectal excision was performed to a level at least 5 cm distal to the tumour. All other patients had a TME.

The operations were performed shortly after the introduction of TME and often by surgeons in training; however, a senior surgeon always participated.

Symptoms of bladder function were assessed before and 3 months after the operation using a questionnaire slightly modified from the International Prostatic Symptom Score. Patients were asked to grade symptoms related to both the storage and evacuation functions of the lower urinary tract on a 100-mm visual analogue scale (VAS). Sexual function was evaluated before and 6 months after the operation, with VAS scoring of sexual activity, libido, potency, ejaculation and dyspareunia. The surgeon explained how to use the VAS, in addition to which patients received written information. To avoid any confusion, all answers were checked by a urologist together with the patient after completion of the questionnaires.

The urodynamic techniques, definitions and units conformed to the standards recommended by the International Continence Society[20]. Before and 3 months after operation patients completed frequency/volume charts for 3 days, and urodynamic examinations were performed. Measurement of urinary flow and residual urine volume, with the patient in the standing position, was performed first. Cystometry and bladder pressure measurements during micturition were performed with the patient in the supine position. The bladder was filled with water (room temperature) at a rate of 50 ml/min using a Lofric (Astra Tech, Mölndal, Sweden) transurethral catheter. A 6-Fr pressure sensor microtip catheter was introduced through the Lofric catheter, and pressure and volume curves were recorded using an Ellipse 4 apparatus (Andromeda, Taufkirchen, Germany). True detrusor pressure was determined by automatically subtracting intra-abdominal pressure, estimated by means of a small balloon recording pressure in the rectum, or in the vagina in women who had been subjected to APR. The intravesical pressure at peak flow and peak flow rate were measured, and detrusor pressure and residual urine volume were calculated. All the curves were later reviewed and checked by a urologist. If abnormalities were found at 3 months, the urodynamic examinations and symptom scoring were repeated 6–9 months after the operation.

Urodynamic investigation was performed successfully in 49 patients before and in 35 patients after operation. Two patients who had signs of bladder denervation before operation were not examined afterwards and seven patients did not want to participate in the examination. In four men who had APR or a very low Hartmann procedure, examination with a rectal probe was impossible and in one patient the examination was technically unsuccessful. However, all patients had spontaneous flowmetry and residual volume of urine measured after operation.

Patient characteristics, including tumour classification, surgical factors and pathology, were recorded. It was also noted whether or not the surgeons were able to identify the autonomic nerves visually: the hypogastric nerves with their origin from the hypogastric plexus at the aortic bifurcation and running down on each side of the pelvis to the pelvic plexus, and the pelvic splanchnic nerves (nervi erigentes) from S2–S4 travelling on the posterolateral pelvic wall. At the end of the operation, the nerves were again visualized and checked for any damage.

For evaluation of the results, each patient served as his or her own control and differences in the symptom scores and objective parameters were calculated. The Wilcoxon signed rank test and Fisher's exact test were applied for statistical analysis. Data were collected and stored in a database, Microsoft Access version 2.0 (Microsoft Corporation, Redmond, Washington, USA), and all statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 8.0 (SPSS, Chicago, Illinois, USA).

Table 1 Type of operation and tumour stage in 49 patients

					Tumour stage			Anastomosis	
	Men	Women	TME	PME	T_2	T_3	T_4	Low	High
LAR	22	13	25	10	12	22	1	24	11
APR	3	6	9		3	5	1		
Hartmann	2	3	5		0	5	0		
Total	27	22	39	10	15	32	2	24	11

High anastomosis, level 7–11 cm from anal verge TME, total mesorectal excision; PME, partial mesorectal excision, LAR, low anterior resection; APR, abdominoperineal resection

Table 2 Urinary function before and after operation

		Men		Women	
	n	Before	After	Before	After
Detrusor pressure at peak flow (cmH_2O)	35	47 (17–75)	45 (25–68)	23 (5–44)	27 (1–60)
Peak flow rate (ml/s)	49	13 (2–26)	13 (6–27)	18 (5–42)	14 (1–26)
Residual volume of urine (ml)	49	27 (0–150)	32 (0–130)	68 (0–250)	58 (0–230)

Values are mean (range)

The study was performed according to the Helsinki Declaration, and approved by the regional ethical research committee. Written informed consent was given by all patients.

Results

Preoperative urinary function

Two of 22 women had a low detrusor pressure, reduced flow rate and increased residual volume, suggesting bladder denervation, one of whom reported no symptoms. Three other women had a slight increase in residual volume of urine, but a detrusor pressure within the normal range. Four of the 27 men showed signs of bladder outlet obstruction, but only two reported symptoms. Forty patients had completely normal preoperative urinary function test results (*Table 2*).

Nerve identification at operation

The operating surgeons were able to identify the hypogastric nerves in 47 of 49 patients. In two patients, inadvertent injury to the hypogastric nerves was recognized. The pelvic nerves were clearly identified in 26 patients and no injuries were apparent.

Postoperative urinary function

The bladder catheter was removed 2–25 (median 7) days after operation. Three months after operation, two women reported difficulty with bladder emptying, and were shown to have signs of bladder denervation, with a weak detrusor pressure, reduced flow and increased residual volume. One of these patients had a T_4 tumour in the mid rectum, and LAR was combined with hysterectomy, resection of the upper part of the vagina and a wide excision of tissue on the anterolateral side of the rectum. The other patient had recovered fully within 9 months of the operation.

The remaining patients had no significant changes in detrusor pressure, peak flow rate or residual volume of urine (*Table 2*). In 14 patients who did not have a urodynamic examination after operation, there were no differences in spontaneous flow rate or residual urine volume before and after the operation.

Table 3 Sexual function in 27 men

	Before operation	After operation
Fully sexually active	10	6
Reduced activity	9	12
Not active	8	9
Normal erection	14	10
Reduced erectile function	10	13
Impotent	3	4
Retrograde ejaculation	1	3

There were no significant changes in the symptom scores, except for an increase in urinary incontinence in women ($P = 0.03$). Four women, without signs of bladder denervation, reported moderate incontinence after the operation (VAS score reduction from 95–100 to 65–70), but these symptoms resolved with time.

Sexual function

Six women were sexually active before the operation and, while they remained active after the operation, three reported reduction of libido and sexual activity by approximately 50 per cent. The effect of operation on sexual function in 27 men is summarized in *Table 3*. One man, who had liver metastasis and received cytostatic therapy after operation, became impotent. Six other men reported some reduction in erectile function after the operation (VAS score reduction by approximately 50 per cent), but were still sexually active. Three of five men who underwent APR or a low Hartmann procedure, and four of 15 who had LAR, reported reduction in erectile function. Two men developed retrograde ejaculation after the operation, in one of whom damage to the hypogastric nerves was identified during operation; in the other the nerves and nerve plexus were not identified. Both of these patients also had some reduction of erectile function.

Total *versus* partial mesorectal excision

All of the patients who developed postoperative bladder and sexual dysfunction were among the 39 who underwent TME. None of the ten patients who had a partial mesorectal excision had such complications.

Discussion

The important finding in this study was that only two women developed signs of bladder denervation after rectal excision, in one case the result of radical excision of a locally advanced tumour. These results compare favourably with those of other studies, which report an incidence of bladder denervation varying from 8 to 54 per cent[1,11,18,19,21–23]. However, operative technique differed between studies, and in some was not described precisely.

Four women had moderate urinary incontinence after the operation, which disappeared within 4 months. The cause of this is unknown, but minor nerve injuries affecting the intrinsic urethral sphincter may be an explanation[10,24]. Urinary dysfunction after rectal cancer operations is often transitory. The cause may be temporary nerve injury caused by traction or diathermy injury, or incomplete division of nerves that later regenerate[25].

To the authors' knowledge, this is the first urodynamic study in patients undergoing mesorectal excision. Bladder pressure measurement during micturition is the most reliable method of identifying bladder denervation. In four patients, major disturbances in detrusor function were identified before operation which could easily have been overlooked without preoperative pressure–flow examination. These findings emphasize the importance of performing urodynamic investigations both before and after operation[18,19,21].

Sexual function cannot be assessed by objective tests, and the results of recording of symptoms with questionnaires should be interpreted with caution. Few of the female patients were sexually active, and no conclusions can be drawn. Only one of 24 men became impotent and had to give up sexual activity after the operation. Retrograde ejaculation occurred in two sexually active patients. Six other patients reported some erectile dysfunction after the operation, but were still sexually active. Factors other than nerve injury, especially psychological, might play a role in these cases. In several studies the frequency of impotence has been reported as from 11 to 76 per cent, and the incidence of retrograde ejaculation from 17 to 70 per cent[2,4,7,12–14,26,27]. By comparison, the present study seems to indicate that nerve injury leading to serious sexual dysfunction is infrequent after mesorectal excision.

The technique of TME for cancer was introduced in Norway in 1992. The main reason was an unacceptably high rate of local recurrence following the conventional technique employed previously[17]. TME as described by Heald requires sharp dissection within the true pelvis, visualization and, if possible, preservation of the autonomic nerves and dissection in the 'holy plane' outside the visceral pelvic fascia around the fatty mesorectal tissue[15]. Since the main cause of postoperative genitourinary dysfunction is autonomic nerve injury, one would expect a low frequency of such complications after properly performed TME. This study confirms that the incidence of permanent urinary and sexual dysfunction is low. This was achieved shortly after introduction of the TME technique, and indicates that nerve-sparing surgery for rectal cancer can be mastered within a short time. The oncological results after TME are promising, and the low frequency of genitourinary complications further supports the contention that mesorectal excision should be the standard treatment for rectal cancer. There were no cases of genitourinary dysfunction after partial mesorectal excision, and this is the preferred method for patients with carcinoma in the upper rectum.

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Original article

Prolonged ambulatory recording of antroduodenal motility in slow-transit constipation

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Background: Slow-transit constipation may be part of a pan-enteric motor disorder. To test this hypothesis 24-h ambulatory antroduodenal manometry was performed and orocaecal transit time determined in patients with slow-transit constipation and in healthy controls.
Methods: Antroduodenal motility was recorded with a five-channel solid-state catheter. Postprandial motility was recorded after consumption of two standardized test meals and interdigestive motility was recorded nocturnally. Manometry tracings were analysed for quantitative and qualitative abnormalities. Orocaecal transit time was determined by means of the lactulose hydrogen breath test.
Results: Postprandial motility was no different between patients and controls. However, some minor changes of interdigestive motility were observed. The proportion of phase II activity of the nocturnal cycles of the interdigestive migrating motor complex was increased in patients while phase I activity was decreased. The total number of observed phase III fronts was no different in patients and controls, although the number of phase III fronts with antral onset was decreased. Furthermore, the amplitude of phase III activity of duodenal onset was also decreased. Specific motor abnormalities such as retrograde propagation of phase III fronts were more frequent in patients. Orocaecal transit time was delayed in patients.
Conclusion: In patients with slow-transit constipation, orocaecal transit time is delayed but antroduodenal motility is generally well preserved with only minor alterations.

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Introduction

Idiopathic slow-transit constipation (STC) is a disorder that affects mainly young women[1] and has a low response to conservative medical treatment. Apart from lower abdominal symptoms, patients with STC frequently complain of upper gastrointestinal symptoms such as bloating, nausea, heartburn, postprandial fullness and pain.

Until recently, idiopathic STC was considered a disorder confined to the colon. Patients with otherwise intractable STC were referred to the surgeon with the request to perform a (sub)total colectomy in order to alleviate symptoms. However, the outcome of this surgical procedure remains highly variable; although stool frequency improves in the majority of patients with STC, upper gastrointestinal symptoms persist in a considerable number of patients[2–5]. Consequently it has been suggested that STC might be part of a pan-enteric disorder[5]. To date, proximal gastrointestinal function in patients with STC has been investigated and alterations in oesophageal motility[6], delayed gastric emptying[6–8] and abnormal small bowel motility[8–12] have been observed. Small bowel motility was evaluated only for short intervals or without including a postprandial period.

The aim of this study was to investigate whether antroduodenal motility is altered in patients with STC in comparison to healthy controls by performing 24-h antroduodenal manometry in an ambulatory setting including both interdigestive and postprandial periods. In addition, orocaecal transit time (OCTT) was determined and compared with the manometry results.

Patients and methods

Subjects

STC was defined by a stool frequency of two times per week or less, persistent for at least 12 months. Patients who had previously undergone abdominal surgery were excluded.

Patients were screened for outlet obstruction by means of defaecography[13] and electromyography[14], and excluded if outlet obstruction was present. Large bowel transit was determined according to the method of Wald[15]. Colonic transit was considered delayed when the residual number of ingested markers in the colon on day 5 was 20 per cent or more of the 50 ingested markers. According to these criteria and the results of the colonic transit time, 30 patients with STC were included: 27 women and three men with a mean(s.e.m.) age of 45(3) (range 16–71) years.

All patients had a long-standing history of severe constipation (mean(s.e.m.) duration 17(3) years). They regularly used oral laxatives or enemas. Mean(s.e.m.) stool frequency without the use of laxatives was 1·4(0·1) times per week. Mean(s.e.m.) large bowel transit time was 107(4) h. Most patients (70 per cent) suffered from proximal gastrointestinal symptoms such as nausea, vomiting and fullness.

The control group consisted of 20 women and two men. None was on medication or had a relevant medical history. All control subjects reported a normal bowel frequency and none had a history of constipation or diarrhoea. The mean(s.e.m.) age of the controls was 39(3) (range 21–63) years. Mean(s.e.m.) large bowel transit time in the control group was 37(3) h.

All subjects gave informed consent and the local human ethics committee approved the study protocol. Patients with constipation were instructed to stop any medication that might interfere with gastrointestinal motility at least 3 days before the test. They were instructed to defaecate, if necessary with the use of enemas, on the day before the measurements.

Equipment

Antroduodenal motility was recorded using a five-channel solid-state catheter assembly (Sentron, Roden, The Netherlands), with pressure sensors located at 3, 8, 13, 28 and 33 cm from the distal tip. The catheter was connected to a portable data logger (Microdigitrapper; Synectics Medical, Stockholm, Sweden) with a storage capacity of 4 MB. The sampling frequency of the recording was 4 Hz.

Study design

After a fasting period of 5 h, subjects were intubated at 17.00 hours on day 1. The catheter was inserted transnasally into the stomach and positioned under fluoroscopic control so that the distal tip was located at the ligament of Treitz, with three sensors in the duodenum and two in the antrum. At 18.00 hours subjects consumed a 1093-kcal dinner (40 g protein, 42 g fat and 139 g carbohydrate). After finishing this meal, subjects received instructions and were allowed to go home. From 23.00 hours on day 1 to 07.00 hours on day 2, subjects were in a supine position and slept or otherwise rested. A 640-kcal breakfast (12 g protein, 22 g fat and 88 g carbohydrate) was consumed at 08.00 hours on day 2. Subjects were allowed to drink a cup of tea or coffee at 20.00 and 21.00 hours on day 1 and at 08.00 and 09.00 hours on day 2. When thirsty, they were allowed to drink 150 ml tap water per hour. At 15.00 hours on day 2, the catheter was removed after fluoroscopic confirmation of its position.

Data analysis

Motility patterns were processed by the software program Polygram (Synectics Medical, Stockholm, Sweden) in order to extract artefacts and to adjust baselines. Antral motility was analysed using the pressure tracings recorded from the most proximal sensor (33 cm from the distal tip); duodenal motor characteristics were analysed using the pressure tracings recorded from the pressure sensor located most proximal in the duodenum (13 cm from the distal tip). Manometry tracings were quantitatively analysed both visually and by computer, as described in detail previously[16–18]. In addition, all manometry recordings were analysed visually for previously described specific motor abnormalities[9].

Hydrogen breath test

On a separate test day, OCTT was measured[19] by means of 12 g lactulose (Legendal; Zambon Nederland, Amersfoort, The Netherlands). OCTT was defined as the time between ingestion of the lactulose and the observation of a sustained increase of breath hydrogen of at least 10 p.p.m. above basal. Non-hydrogen producers[20] were excluded from analysis.

Statistical analysis

Results are expressed as mean(s.e.m.). Statistical comparisons were made using the non-parametric Mann–Whitney rank sum test or, where appropriate, Student's t test for unpaired data. Differences of onset of phase III (antrum or duodenum) were determined by χ^2 analysis of contingency tables. After subdivision of the fed pattern into separate 60-min intervals, between-groups parameters of the 60-min intervals were compared using the non-parametric Mann–Whitney rank sum test or, where appropriate, by analysis of variance with Bonferroni's correction for multiple comparisons. $P < 0·05$ was considered statistically significant.

Results

The mean(s.e.m.) recording time was similar in the control and patients groups (21·8(0·1) *versus* 21·5(0·2) h respectively).

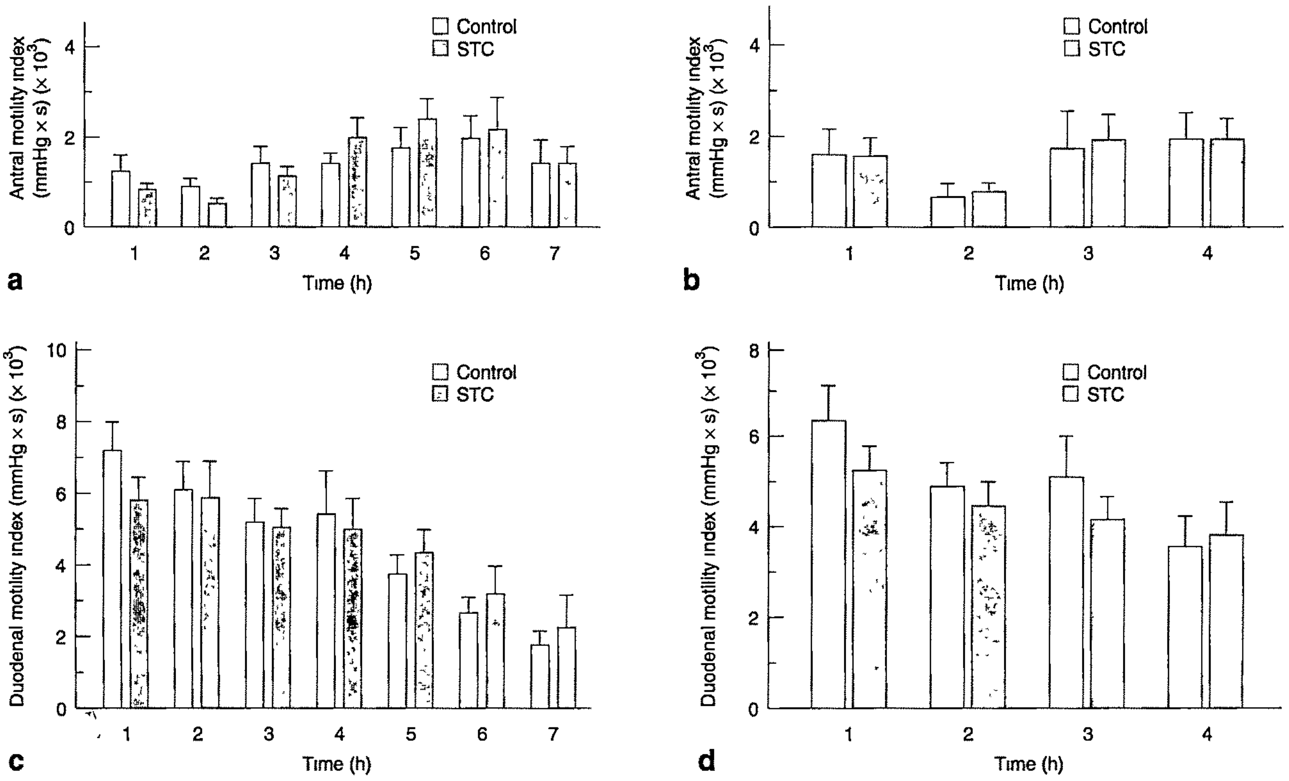

Fig. 1 Mean postprandial antral and duodenal motility index in 22 control subjects and 30 patients with slow-transit constipation (STC): **a** and **c** during the first 7 h of the evening fed pattern; **b** and **d** during the first 4 h of the morning fed pattern

Postprandial motility

The characteristics of the fed patterns induced by dinner and breakfast are shown in *Table 1*. No significant differences were observed between patients and controls. Motility parameters were also compared in 1-h periods of the fed patterns after dinner and breakfast. *Fig. 1* displays mean antral and duodenal motility indices for each hour for both fed patterns. In patients with STC, the antral motility index was reduced, although not significantly, during the first 3 h of the evening fed pattern and increased thereafter. The duodenal motility index was no different between patients and controls.

Interdigestive motility

The mean(s.e.m.) duration of the nocturnal interdigestive period in the controls was 6·3(0·3) h *versus* 6·7(0·4) h in

Table 1 Characteristics of fed patterns induced by dinner and breakfast

	Dinner		Breakfast	
	Control	STC	Control	STC
Duration (min)	449(19)	444(23)	270(17)	271(15)
Antrum				
Frequency (per min)	1·0(0·2)	0·7(0 1)	0·9(0·3)	0·7(0 1)
Amplitude (mmHg)	26·7(2·4)	32·2(2·4)	34·2(3·7)	36·6(3·3)
Motility index (mmHg × s)*	13 837(2281)	13 281(2042)	10 893(1787)	12 436(2356)
Duodenum				
Frequency (per min)	2·8(0·2)	2·6(0·2)	3 2(0·3)	2 9(0 3)
Amplitude (mmHg)	23·3(0·8)	23 2(0·7)	23 4(0·7)	22·8(0 8)
Motility index (mmHg × s)*	32 729(3399)	33 816(5186)	22 432(2610)	19 798(2138)

Values are mean(s.e.m.). STC, slow-transit constipation. *Motility index of total fed pattern

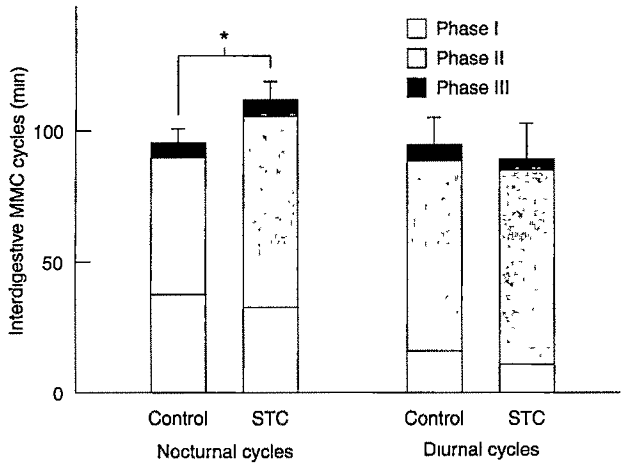

Fig. 2 Mean length and phase distribution of nocturnal and diurnal interdigestive migrating motor complex (MMC) cycles in 22 control subjects and 30 patients with slow-transit constipation (STC). *$P < 0{\cdot}05$ *versus* control (analysis of variance)

patients (*P* not significant). The characteristics of nocturnal and diurnal interdigestive migrating motor complex (MMC) cycles are displayed in *Fig. 2*. Nocturnally, the mean number of complete MMC cycles per subject was no different between patients with STC and controls (3·3(0·3) *versus* 3·5(0·3) respectively), while MMC cycle length was prolonged in patients (*P* not significant). The phase distribution of these MMC cycles was altered in patients with STC compared with controls: the duration of phase I activity was reduced, in terms of both duration (min) (*P* not significant) and proportion ($P < 0{\cdot}05$), and phase II activity was prolonged ($P < 0{\cdot}05$). Diurnally, no differences were observed in phase distribution of the MMC cycles. When nocturnal and diurnal MMC characteristics in the control group were compared, phase I was reduced and phase II activity was increased diurnally (all $P < 0{\cdot}05$). In the patient group, these differences were also observed. *Fig. 3* displays manometry tracings from a patient with STC recorded during nocturnal (*Fig. 3a*) and diurnal (*Fig. 3b*) interdigestive periods, demonstrating the difference between nocturnal and diurnal MMC phase distribution.

Phase III motor fronts

The total number of phases III of duodenal origin was no different between patients and controls (4·0(0·6) *versus* 3·5(0·4) respectively), but the number of phase III fronts of antral origin was significantly reduced in patients (1·8(0·2) *versus* 3·0(0·4) in controls; $P < 0{\cdot}05$). *Table 2* gives the duodenal characteristics of nocturnal and diurnal phase III motor fronts of antral and duodenal origin. In patients with STC, the duration of antral phase III was significantly shortened nocturnally. Furthermore, the mean amplitude

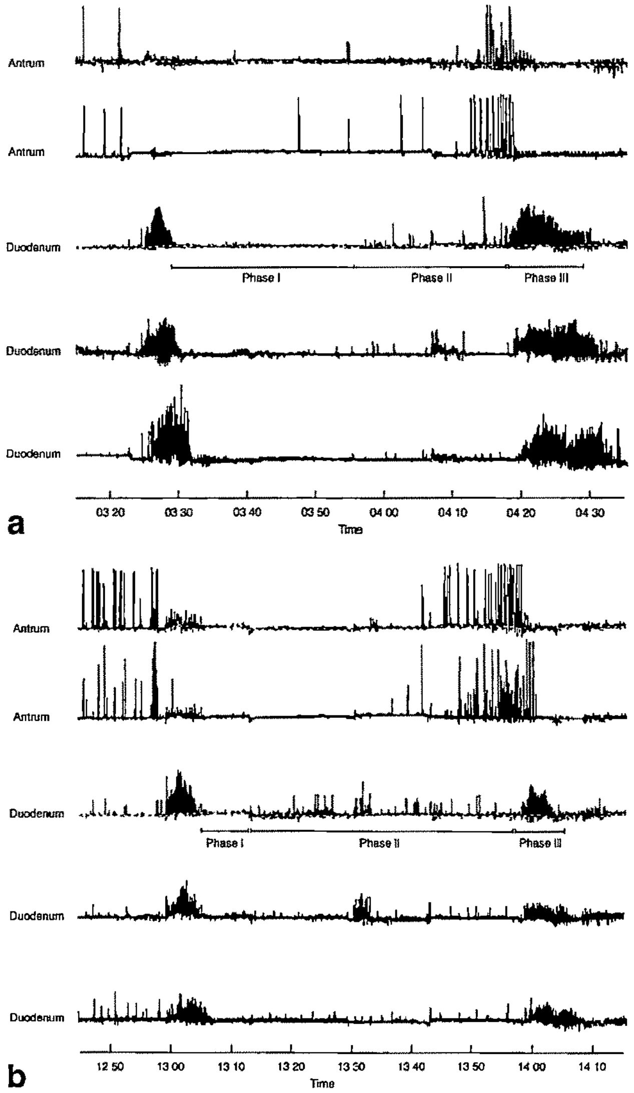

Fig. 3 **a** Normal nocturnal and **b** normal diurnal fasting antroduodenal motor activity recorded from a patient with slow-transit constipation. Simultaneous recording of antral (top two channels) and duodenal (lower three channels) motor activity, illustrating interdigestive cycles of the migrating motor complex

of phase III activity of duodenal onset was significantly reduced diurnally and nocturnally in the patient group.

Qualitative analysis

The proportion of time for each subject for which bursts of non-propagated activity occurred was no different between patients and controls (1·0(0·7) *versus* 1·0(0·3) per cent respectively). The proportion of time per subject in which discrete clustered contractions (DCCs) occurred ($P = 0.03$) was significantly increased in patients with STC compared

Table 2 Characteristics of nocturnal and diurnal phase III motor fronts in the duodenum

	Duration (min)	Frequency (per min)	Amplitude (mmHg)	Motility index (mmHg × s)	Velocity (mm/s)
Nocturnal fronts					
Antral origin					
Control	7·5(0·5)	11·6(0·7)	31·2(2 0)	3683(431)	3·53(0 68)
STC	6·3(0 4)*	11·1(0·1)	29 8(1·8)	3090(325)	2·81(0·53)
Duodenal origin					
Control	4·3(0 4)	11·2(0 1)	30 8(2·7)	2179(318)	4·12(1·04)
STC	4·6(0·3)	11·5(0·6)	26·6(1·7)*	1676(297)	3·64(0·64)
Diurnal fronts					
Antral origin					
Control	5·1(0 6)	11·2(0·2)	31 3(2·2)	2746(457)	2·78(0·99)
STC	4 7(0·6)	11·5(0·3)	36·1(4 3)	2369(373)	2·71(0·41)
Duodenal origin					
Control	3·5(0·3)	11·5(0 2)	34·0(3·2)	1913(295)	3·57(0 67)
STC	3·8(0·2)	10·5(0·5)	26·9(2·3)*	1316(164)	4 51(0·93)

Values are mean(s.e.m.) STC, slow-transit constipation. *$P < 0\ 05$ *versus* control (analysis of variance)

with controls (4·6(1·0) *versus* 2·0(0·4) per cent). The total number of phase III motor fronts observed was no different between patients and controls. However, the mean number of observed retrograde phase III motor fronts ($P = 0{\cdot}041$) was significantly increased in patients with STC compared with controls (0·3(0·1) *versus* 0·0(0·0)).

Orocaecal transit time

The mean OCTT was significantly prolonged in the patient group (108(9) *versus* 78(6) min in controls; $P < 0{\cdot}05$). No correlation was observed between OCTT and MMC cycle duration, the number of phase III motor fronts, percentage phase II activity or the percentage time in which DCCs occurred. In addition, motility parameters were no different when a comparison was made between patients with OCTT of less than 120 min and those with OCTT of 120 min or more.

Subgroup analysis

Based on parameters of antroduodenal motility and the hydrogen breath test, it was not possible to recognize a subgroup of patients with STC with generalized abnormalities. In addition, there was no correlation between the results of tests and clinical parameters such as duration of constipation, defaecation frequency or colonic transit time.

Discussion

In patients with STC antroduodenal motility is generally well preserved with only minor alterations. The main differences observed between patients and controls were altered phase distribution of the nocturnal interdigestive MMC cycles and a reduction of the number of phase III fronts with antral onset.

Postprandial antroduodenal motility was not altered in STC. The duration of the fed pattern was no different, but antral motility was slightly reduced in the early postprandial phase. These findings contrast with those of other studies which have described a shorter duration of the fed pattern measured in either the duodenum[8] or the terminal ileum[10] of patients with STC. This discrepancy might be due to differences in the composition and size of the test meals or to differences in the number of patients studied. Recently, Bassotti *et al.*[9] demonstrated that the duration of postprandial antral motor activity was reduced in patients with STC, which is in line with the present findings of a reduced antral motility index during the first 3 h after dinner.

In patients with STC delayed gastric emptying is frequently observed[6–8]. It may be secondary to antral hypomotility, but also to small intestinal dysmotility, impaired antroduodenal coordination[21] or altered function of the proximal stomach[22]. The present study demonstrates that antral hypomotility is not present in patients with STC. Although antral motility index was slightly reduced during the early postprandial phase, overall postprandial antral motility index was not different. Small intestinal dysmotility, which is characterized by increased numbers of aberrantly propagated or configured phase III fronts and frequent bursts of non-propagated phasic pressure activity[21], was not found in patients with STC. Delayed gastric emptying may be secondary to disturbed antroduodenal coordination or altered relaxation of the proximal stomach.

This study demonstrated a slightly prolonged MMC cycle length and altered phase distribution in patients with STC. Prolonged duration of the MMC cycle and phase II in STC has been reported by others[8,10,11]. The total number of phase III fronts was reduced, although not significantly, which corresponds with the findings of Coremans *et al.*[8]. The qualitative analysis of manometry tracings indicated that the number of phase III fronts with retrograde propagation was significantly increased in patients with STC. DCCs were also more frequent. Both findings correspond with the observations of others[9,12].

Previous studies have described several other abnormalities of antroduodenal motility in patients with STC, which were not confirmed by the present study. Examples are an increased frequency of bursts of non-propagated phasic pressure activity[9,12] and reduced MMC cycle length[11]. These differences might be secondary to the measurement technique, for example stationary *versus* ambulatory manometry, duration of the recording, group size and the rate of standardization of the recording, such as the incorporation of standardized test meals. The present study involved measurement of antroduodenal motility for a prolonged period in an ambulatory setting, which allowed the recording of nocturnal interdigestive MMC cycles, which are relatively free from artefact. In addition, the study incorporated two standardized test meals and involved a large group of patients. Manometry was performed 1 day after defaecation, whereas other studies did not state whether patients were studied while constipated or after defaecation. Thus, the alterations described in several studies might also be due to prolonged stasis. OCTT was significantly prolonged in patients with STC, as reported by others[20,23,24]. OCTT is mainly determined by MMC cycle length and therefore by the number of phase III fronts from duodenum to ileum, and to a limited extent by the rate of gastric emptying[25]. The motility study demonstrated that MMC cycle length is slightly prolonged and that the amplitude of phase III activity of duodenal onset is reduced. These factors might contribute to prolonged small bowel transit time, although it is also possible that prolonged OCTT in patients with STC is due to alterations in jejunal or ileal motility[10].

The clinical relevance of measuring antroduodenal motility in patients with STC seems limited: although all patients suffered from long-standing severe constipation, antroduodenal motility in general was well preserved. In addition, it was not possible to subdivide the patients with STC into subgroups with normal or abnormal manometry results based on clinical parameters such as severity or duration of symptoms.

Apart from delayed gastric emptying and delayed colonic transit time, transit through the small intestine is also delayed in patients with STC, indicating that the condition is part of a more generalized gastrointestinal motor disorder. Since antroduodenal motility is regulated by circulating gastrointestinal hormones such as motilin and cholecystokinin[26–28], and to a lesser extent by extrinsic innervation such as the vagus nerve[28,29], the observed (minor) changes in antroduodenal motility might point to alterations in vagus nerve function, or to abnormal levels of circulating gastrointestinal peptides, such as plasma motilin, in these patients. Fasting and meal-induced plasma motilin levels are reduced in patients with STC[30], which may be in line with the reduced number of phase III fronts of antral origin observed.

It is concluded from this study that antroduodenal motility is generally well preserved in patients with STC. The delay in OCTT might indicate that motility of the distal small bowel (i.e. the jejunum or ileum) is altered in STC.

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Original article

Evaluation of Delorme's procedure as a treatment for full-thickness rectal prolapse

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Background: Delorme's procedure is a well tolerated perineal operation for full-thickness rectal prolapse. However, prolapse recurrence is common and reported recurrence rates vary widely. This study attempted to standardize outcome assessment for recurrence following primary and subsequent Delorme's operations. Patient and operative factors were analysed to identify any that might improve patient selection.

Methods: Some 101 primary and 17 secondary Delorme's procedures were carried out on 113 consecutive patients presenting with rectal prolapse, who were followed for a minimum of 12 months, unless death or recurrent prolapse intervened. The rate of prolapse recurrence was calculated using the Kaplan–Meier method of analysis. Patient age, sex, grade of incontinence, presence of diverticular disease, length of mucosal resection and position in the operative series were analysed to identify factors affecting recurrence.

Results: The predicted recurrence-free period for 50 per cent of patients undergoing primary and secondary Delorme's procedures was 91 (95 per cent confidence interval 77–105) and 27 (15–39) months respectively. None of the patient or operative factors analysed was related to recurrent prolapse.

Conclusion: Delorme's procedure is a simple operation with satisfactory functional results which can be considered in all patients of all ages. However, high recurrence rates for primary and repeat operations should be explained to patients when planning their surgical management.

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Introduction

Delorme's procedure is a perineal technique for repair of full-thickness rectal prolapse, first described by the French military surgeon Edmond Delorme in 1900[1]. The operation was initially seen to be technically simple and safe. However, it fell into disfavour after anecdotal reports of high recurrence rates, and high postoperative morbidity and mortality rates[2].

In the past 20 years its popularity has re-emerged. Improved techniques have made it a relatively safe procedure that is ideal for those not fit enough to withstand an abdominal operation. Recent series of Delorme's procedures still report high recurrence rates[3,4], although, in contrast to certain abdominal procedures[5], it is not associated with significant postoperative constipation. The simplicity of approach and lack of major complications have made it popular with both surgeons and patients, and led to its use as a repeat as well as primary operation for rectal prolapse.

The difficulty of assessing outcome in an elderly population has contributed to the wide range of published results from different series[3,4,6–10]. Furthermore, little is understood about the factors associated with recurrence. The aim of this study was to determine the recurrence rates and functional results following primary and repeat Delorme's procedures in patients who were followed for at least 1 year.

Patients and methods

From November 1983 to June 1994, 113 consecutive patients presenting to one surgeon with full-thickness rectal prolapse were treated by Delorme's procedure. Nineteen of the patients had a second and three patients a third Delorme's procedure following prolapse recurrence, making 135 operations in total.

Preoperative assessment

Data were collected prospectively or, where this was not possible, hospital notes were reviewed retrospectively.

Complete details, including use of faecal incontinence pads, medication and sigmoidoscopy findings were recorded for 81 patients. Faecal incontinence was recorded according to the grading system proposed by Browning and Parks[11] and true constipation was defined as hard stools with a frequency of less than once a day.

Surgical technique

All patients had preoperative disposable enemas and either preoperative or perioperative flexible sigmoidoscopy. Patients in the later part of the series had antibiotic and deep venous thrombosis prophylaxis, administered on induction of anaesthesia. Twenty-two operations were performed under spinal block and two patients were operated on after infiltration with local anaesthetic. All regional techniques were augmented by intravenous sedation and the remaining operations were carried out under general anaesthetic. Patients were positioned in the lithotomy position apart from two, who were placed in the left lateral position because of fixed flexion and adduction deformities of the hip.

Where possible the rectal prolapse and anal canal were everted. A circumferential incision was made with cutting diathermy approximately 1·5 cm proximal to the dentate line and the mucosa was released from the underlying muscularis mucosae to produce a cylinder that could be held under tension.

Occasionally the anal canal could not be everted before stripping, so the initial dissection was performed endoanally using 30–40 ml normal saline containing adrenaline 1 : 200 000. The mucosal cylinder narrows as it develops, increasing the risk of buttonholing. At this point it became safer to continue the dissection with scissors rather than diathermy.

The dissection was complete when the prolapse could not be externalized beyond the anal verge. The denuded muscle was plicated with four 2/0 polyglactin 'anchor' sutures placed equally around the anal ring. The mucosal tube was divided from the rectal stump and further sutures were inserted into each quadrant. In 17 patients with very poor pelvic floor musculature a posterior sphincteroplasty was also performed.

Free fluids and solid food were allowed *ad libitum* immediately after operation. When bowel function returned most patients developed urgency and frequent loose stools with incontinence, requiring a low-roughage diet, codeine phosphate and anal barrier cream. In most patients, hospital stay was limited only until the bowels were opened successfully or by social problems.

Postoperative follow-up

Patients were followed yearly, until recurrence of the prolapse or death intervened. When this was not possible the patient, general practitioner or carer was contacted directly. On each occasion, the state of the rectal prolapse was assessed along with anal sphincteric tone. The patients were questioned about their use of drugs to moderate bowel function, consistency of the stools, grade of faecal incontinence and use of incontinence pads.

The mean follow-up was calculated for all patients as the total period of time for which they were monitored or the recurrence-free interval if this was less. Patients were excluded from the final analysis if the follow-up period was less than 12 months or if the patient was lost to follow-up and the final outcome not known, unless recurrence or death occurred before this.

Statistical analysis

Kaplan–Meier plots were used to calculate the probability of non-recurrence for each parameter examined. The probabilities were compared using the pairwise log rank statistic. The risk of recurrence was calculated by Cox regression, and its constancy over time confirmed by log minus log plots. Student's *t* test was used to analyse the changes in bowel function before and after operation. All statistics and plots were created using the software package SPSS version 9.0 (SPSS, Chicago, Illinois, USA).

Results

Outcome following primary Delorme's procedure

The outcome was analysed for 101 of 113 patients who underwent Delorme's procedure with postoperative follow-up for a minimum of 12 months, or in whom death or recurrent prolapse intervened (*Table 1*). Mean follow-up for the 101 patients was 36 (range 0–139) months. There were ten men, of mean age 58 (range 25–76) years, and 91 women, of mean age 75 (range 19–92) years. The mean age overall was 73 years and the mean length of the primary mucosal resection was 147 (range 30–490) mm.

Surgical complications

There were four deaths within 30 days of surgery. Two 80-year-old women died 10 and 18 days after operation from myocardial infarction and pneumonia respectively, and one 90-year-old woman with chronic active hepatitis died from

Table 1 Outcome of primary Delorme's procedure

Surgical outcome	No. of patients (*n* = 113)*	Recurrence-free interval (months)†	Follow-up (months)†
No recurrence	38 (34)		56 (18–139)
Died with no recurrence	33 (29)		26 (0–116)
Recurrent prolapse	30 (27)	23 (0–134)	
Follow-up < 12 months	12 (11)		

*Values in parentheses are percentages; †values are mean (range)

Table 2 Outcome of a second Delorme's procedure

Surgical outcome	No. of patients (*n* = 19)	Recurrence-free interval (months)*	Follow-up (months)*
No recurrence	5		39 (25–55)
Died with no recurrence	3		5 (1–12)
Recurrent prolapse	9	8 (0–20)	
Follow-up < 12 months	2		

*Values are mean (range)

severe haemolytic anaemia. In only one patient was death associated with a surgical complication, 30 per cent anastomotic dehiscence. Another patient suffered severe postoperative constipation requiring a colectomy and temporary colostomy.

Repeat operations

Thirty patients developed a recurrent prolapse. One has undergone a Well's abdominal rectopexy, two patients have since died from unrelated causes, four are awaiting a further Delorme's operation and four do not have symptoms requiring further surgical intervention.

Nineteen patients underwent a second Delorme's operation, but two patients have been excluded from the analysis since it has not been possible to monitor the outcome of surgery beyond the first 12 months (*Table 2*). The remaining 17 patients were followed for a mean of 16 (range 0–55) months. There were 16 women, of mean age 75 (range 55–91) years, and one man aged 79 years. The mean length of the second mucosal resection was 107 (range 40–200) mm. Three patients have undergone a third operation. One suffered recurrence after 11 months and two are recurrence free after 23 and 7 months, both with good bowel function.

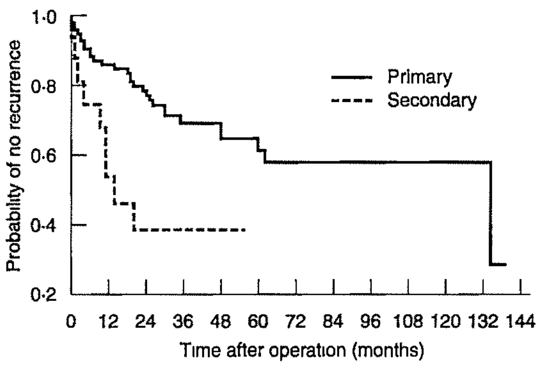
Changes in bowel function following Delorme's procedure

Following primary surgery 35 per cent of patients were completely continent (grade 1) compared with 10 per cent before operation. Overall 72 (89 per cent) of 81 patients showed static or improved levels of faecal continence ($P < 0.001$). After a second Delorme's procedure, the grade of incontinence was the same or improved in 15 of 17 patients, despite the high level of recurrence.

Thirty-two patients (40 per cent) who had been using pads before operation no longer required them after surgery. Six patients (7 per cent) who had not been using pads before operation did so afterwards. There was no change in the remaining 43 patients (53 per cent). Constipation affected 16 (20 per cent) of 81 patients before and seven (7 per cent) of 101 patients after operation. In all but one patient the constipation was controlled with laxatives. Nearly all patients had urgent defaecation after operation, which was controlled by a low-roughage diet, codeine phosphate or loperamide. Constipating drugs were used by 26 per cent of patients either intermittently or continuously in the long term.

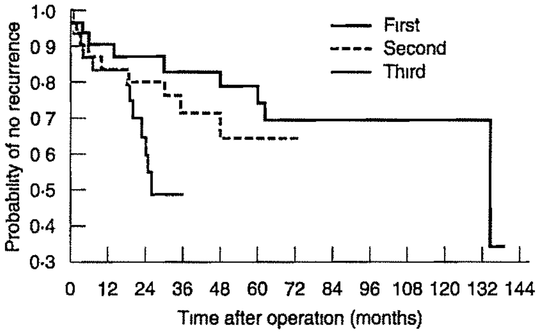
Probability of non-recurrence, and recurrence rates following primary and secondary operations

The predicted recurrence-free period for 50 per cent of patients undergoing primary and secondary Delorme's procedures was significantly different: 91 (95 per cent confidence interval (c.i.) 77–105) and 27 (15–39) months respectively ($P = 0.0038$) (*Fig. 1*). However, the risk of recurrence for both primary and secondary operations remained constant with time. The hazard ratio indicated that the probability of recurrence following a second operation was 1·7 times that following a primary procedure.



No. at risk												
Primary	101	74	61	51	47	44	42	41	40	40	38	38
Secondary	17	7	5	5	5							

Fig. 1 Comparison of probability of no recurrence with time for patients who underwent primary and secondary operations



No. at risk												
First third	34	27	24	20	19	16	15	13	12	12	11	10
Second third	34	23	22	18	15	15	15					
Final third	33	24	14	13								

Fig. 2 Kaplan–Meier plots showing the comparative probability of postoperative recurrence for patients in the three thirds of the primary series

Factors potentially affecting prolapse recurrence

Length of mucosa removed

The mean length of mucosa resected in primary operations from patients whose prolapse did and did not recur was 140 and 145 mm respectively. The corresponding figures for secondary procedures were 105 and 100 mm. Comparison of subgroups of patients in whom the mucosal resection was more or less than 150 mm also showed no significant difference in the probability of recurrence.

Position in the series

Comparison of patients in the three thirds of the operative series demonstrated a significantly smaller probability of non-recurrence by patients included in the final third compared with those in the first ($P = 0.0126$), but not between any of the other subgroups (*Fig. 2*). The mean recurrence-free period for the patients in the first third was 105 (95 per cent c.i. 36–124) months compared with 27 (22–31) months for the final third.

Other factors

Kaplan–Meier analysis showed that older patients and those with high-grade faecal incontinence did not have a significantly decreased probability of non-recurrence with time after operation. Sex, posterior sphincteroplasty and preoperative diverticular disease also had no significant effect on recurrence rates.

Discussion

Rectal prolapse is a distressing and difficult problem for both patient and clinician. The majority of sufferers are elderly, multiparous women, often with associated psychogeriatric problems. Difficulties with patient communication and the effects of coexisting medical conditions complicate outcome assessment. The variety of surgical operations used in the past testifies to the inability of any one technique to provide an adequate solution[12].

Recent series of the Delorme's procedure report a variable recurrence rate of 0–32 per cent[3,4,6–10]. This may be related to the length of follow-up along with variations in case-mix and patient selection. In order to overcome some of these problems, Kaplan–Meier plots were used to measure the probability of non-recurrence over time. This revealed that recurrence following both primary and secondary Delorme's operations is relatively constant over at least 5 years and is significantly greater after a second procedure. This method of analysis may allow more accurate comparison between cohorts of patients from different centres.

In this study, there was an increased recurrence rate in the patients operated on in the third part of the series. This is unlikely to be due to variations in surgical technique, which was not altered over the study period and was the responsibility of a single surgeon. However, it could be due to changes in case-mix, with more severe prolapses referred with time. There were no significant variations in recurrence for any other parameter studied, including the length of mucosa excised. Recurrence was significantly more common following secondary operations, suggesting that prolapses recur in a subgroup of patients who have a more pernicious condition. Delorme added a sphincteroplasty to the procedure in one of his first three patients[1], and this has also been reported in other series[4,6]. Some have claimed that it reduces the rate of recurrence and reported its routine use[4]. There was no evidence of benefit in this study.

Overall, postoperative incontinence is improved by the Delorme's procedure, which is somewhat surprising since it has been shown that there is no change in anal sphincter pressure and there is a reduction in rectal compliance after the operation[13]. The frequent defaecation and tenesmus that occurs following surgery may result from this decreased compliance. In the majority of patients it settles with a low-roughage diet, codeine phosphate and/or loperamide. Consequently, Delorme's procedure has been used as a treatment for constipation[14]. This effect seems to be one of the advantages of Delorme's compared with abdominal procedures, for which constipation has been reported as a serious problem[5], possibly owing to the complete division of the lateral rectal ligaments[15,16]. Rectal mucosectomy may also have an important effect on proximal colonic motility with more frequent rectal filling[13].

Delorme's procedure has been recommended for the frail and elderly. However, it should also be considered as a primary procedure for young women who wish to have a family, those with constipation or patients with a short prolapse and a normal pelvic floor, and in men in whom the risk of impotence following an abdominal procedure is unacceptably high. Repeat Delorme's procedure is associated with a significantly higher incidence of recurrence, which should be taken into account when considering further surgical treatment. Future reports on the surgical treatment of rectal prolapse could be improved by using the Kaplan–Meier method of analysis, rather than using a fixed recurrence rate. This would allow for the comparison of results from series with different periods of follow-up and cohorts of patients with different mortality rates.

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Original article

Lymphocyte activation after non-thermal trauma

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Background: Severe injury causes immunological changes that may contribute to a poor outcome. Longitudinal characterization of lymphocyte response patterns may provide further insight into the basis of these immunological alterations.

Methods: Venous blood obtained seven times over 2 weeks from 61 patients with injury severity scores above 20 was assessed for lymphocyte phenotypic and activation markers together with serum levels of interleukin (IL) 2 , IL-4, soluble IL-2 receptor (sIL-2R), soluble CD4 (sCD4), soluble CD8 (sCD8) and interferon γ.

Results: Severe injury was associated with profound changes in the phenotypic and activation profile of circulating lymphocytes. Activation was indicated by increased numbers of T cells expressing CD25, CD69 and CD71, and raised serum levels of IL-2, sIL-2R, sCD4 and sCD8. Relatively higher levels of sIL-2R and sCD4 were found in patients with sepsis syndrome.

Conclusion: Polytrauma is associated with dramatic alterations in the phenotypic and activation profile of circulating lymphocytes which are generally independent of clinical course. In contrast, several lymphocyte soluble factors, including sCD4 and sIL-2R, paralleled the clinical course. These data provide new insight into lymphocyte responses after injury and suggest that further assessment of soluble factors as clinical correlates, including those related to lymphocyte activation or generalized inflammation, may be warranted.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the US Department of the Army or the Department of Defense.

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Introduction

Immunological alterations associated with severe injury may contribute to a high risk of sepsis. These include reduced blood lymphocyte and monocyte populations, *in vitro* deficiencies in lymphocyte proliferation and skin test anergy[1–9]. However, trauma may also trigger T lymphocyte activation, indicated by increased serum levels of interleukin (IL) 2 and soluble IL-2 receptors (sIL-2Rs), heightened expression of the T cell activation markers CD25, CD69 and CD71, and spontaneous *in vitro* lymphocyte blastogenesis[10–18]. Recent reports suggest that T lymphocytes from injured patients secrete large amounts of 'type 2 T helper (Th) cell-like' cytokines, suggesting that trauma polarizes the lymphocyte response rather than inducing generalized T cell suppression[18–24]. Whether a Th2-like response after trauma would increase the risk of sepsis is unclear[24]. However, some discordance among *in vitro* and *in vivo* observations may in part be due to the Th1–Th2 imbalance, which in turn may reflect the systemic inflammatory response syndrome (SIRS) of non-discriminate immune activation following polytrauma[25,26].

In this study, longitudinal characterization of *in vivo* lymphocyte response patterns was conducted for 2 weeks after severe injury. The data confirm that polytrauma induces profound alterations in the phenotypic and activation profile of circulating lymphocytes. In agreement with previous reports, most changes in lymphocyte phenotypic and cell surface activation status appeared to be independent of clinical course, supporting the notion that biological variability is an important but poorly understood factor in the development of sepsis after injury[27]. However, notable trends between several soluble factors and clinical course, especially soluble CD4 (sCD4) and sIL-2R, suggest that further assessment of these and other soluble inflammatory factors may be warranted in a larger patient cohort.

Patients and methods

Consenting patients aged 18–50 years with an injury severity score (ISS)[28] above 20 were enrolled in the study, which was approved by US Army Scientific and Human Use Research Review Boards and by the ethics committee of each hospital. Patients were assessed daily by clinical research personnel until discharge or death. Clinical outcomes to day 13 were classified as uneventful (to include minor infections without fever or worsening leucocytosis) or sepsis syndrome[29]. Prophylactic parenteral antibiotics were usually administered for several days upon admission and then adjusted depending on clinical signs or culture results. Controls comprised 30 non-injured, age-matched healthy volunteers.

Sample collection

Venous blood, obtained on days 1 (admission), 2, 3, 5, 7, 10 and 13, was placed into Vacutainer tubes containing sodium heparin, sodium ethylenediamine tetra-acetic acid or no additive (Becton Dickinson, East Rutherford, New Jersey, USA) and then transported in a chilled container to the laboratory.

White blood cell count and differential

White cell counts were made by a haemocytometer. Wright-stained differential counts were conducted to calculate the absolute number of cells per microlitre of blood.

Monoclonal antibodies, cell staining and flow cytometry

Fluorescein isothiocyanate (FITC)- or phycoerythrin (PE)-conjugated monoclonal antibodies (Becton Dickinson, San Jose, California, USA) reactive to lineage or activation markers are shown in *Tables 1–3*. Cell isolation and staining were conducted as described previously[30]. For enumeration of T cell subsets and expression of activation markers, a double staining technique was used. Analysis of cell surface immunofluorescence was performed on a FACStar Plus Cell Analyser (Becton Dickinson, San Jose, California, USA). For each stained sample, 10 000 cells were analysed for staining positivity after linear light scatter gating on lymphocytes. The fluorescent distribution was analysed using Consort C30 software (Becton Dickinson). Throughout the study, unstained and mixed FITC and PE Calibrite beads (Becton Dickinson) were used to calibrate the analyser. Results were expressed as the proportion of positively stained cells.

Table 1 Monoclonal antibodies for phenotype analysis

Monoclonal antibody	Specificity
Anti-CD3	$\alpha\beta$+ T cells
Anti-$\gamma\delta$	$\gamma\delta$+ T cells
Anti-CD4	T helper cells
Anti-CD4/anti-CD45RA*	Naive T helper cells
Anti-CD4/anti-CD45RO*	Memory T helper cells
Anti-CD4/anti-CD62L*	Naive/memory T helper cells
Anti-CD8	T suppressor/cytotoxic cells
Anti-CD20	B cells
Anti-CD20/anti-CD38*	Immature B cells
Anti-CD16	Fc III λ receptor (resting NK)
Anti-CD57	Fc III λ receptor (resting NK)
Anti-CD16/anti-CD56*	Cytotoxic NK subset

*Two monoclonal antibodies used for subset analysis. NK, natural killer cell

Table 2 Monoclonal antibodies used to assess T cell activation

Monoclonal antibody	Specificity	'Timing'
Anti-CD69	CD69	Early
Anti-CD25	IL-2 receptor	Mid-range
Anti-CD38	CD38	Late
Anti-HLA-DR	MHC class II molecule	Late
Anti-CD71	Transferrin receptor	Late
Anti-VLA	Very late activation antigen	Late

IL, interleukin; HLA, human leucocyte antigen; MHC, major histocompatibility complex; VLA, very late activation antigen

Table 3 Soluble factors used to assess T cell activation

Soluble factor	Primary source
IL-2	Activated T cells
sIL-2R	Activated T cells
IL-4	Activated T cells
Interferon γ	Activated T/NK cells
Soluble CD4	Activated CD4+ cells
Soluble CD8	Activated CD8+ cells

IL, interleukin; sIL-2R, soluble IL-2 receptor; NK, natural killer

Assays for interleukins 2 and 4

Serum levels of IL-2 and IL-4 were measured by enzyme-linked immunosorbent assay (ELISA) (Intertest 2 and Intertest 4 respectively; Genzyme, Boston, Massachusetts, USA). The lower limits of detection were 2·3 units/ml and 0·045 ng/ml respectively.

Assays for soluble interleukin 2 receptor, soluble CD4 and soluble CD8

Serum levels were measured by ELISA (Cellfree IL-2 receptor, CD4 and T8 test kits; T Cell Sciences, Cambridge, Massachusetts, USA). The lower limits of detection were 50, 12 and 50 units/ml respectively.

Assay for interferon γ

Serum levels of interferon (IFN) γ were measured by radioimmunoassay (Centocor γ-interferon Radioimmunoassay; Centocor Diagnostics, Malvern, Pennsylvania, USA). The limit of detection was 0·1 units/ml.

Delayed-type hypersensitivity skin testing

Skin testing on the anterior forearm was conducted on days 1, 7 and 13 using Multitest CMI (Pasteur Merieux, Lyon, France), an application device preloaded with eight recall antigens: tetanus toxoid, diphtheria toxoid, *Streptococcus pyogenes* (group C), tuberculin (old), *Candida albicans*, *Trichophyton mentagrophytes*, *Proteus mirabilis* and glycerin control. Reactions were 'positive' only if the induration was at least 2 × 2 mm in size.

Statistical analysis

Data were entered into a database and analysed by a blinded operator using SPSS+ (SPSS, Chicago, Illinois, USA) and Statgraphics (Manugistics, Rockville, Maryland, USA). Statistical analyses included the Mann–Whitney *U* test, Kruskal–Wallis analysis of variance and Pearson's χ^2 with Yates' correction. In addition to clinical course, immunological readouts were assessed individually against ISS, surgery, haemoperitoneum and units of blood transfused within the first 24 h of admission.

Results

A total of 88 patients were enrolled in the study. Most had been in a motor vehicle accident, sustaining blunt trauma. Seventeen patients received dexamethasone for head injury and ten died within 5 days from severe mechanical injury, and were excluded from analysis. Demographics of the 61 patients analysed in this study are shown in *Table 4*.

White blood cell count and differential

Leucocytosis was observed throughout the study period. The percentage and absolute number of lymphocytes were significantly reduced in comparison to control values, especially on days 1, 2 and 3. There was neutrophilia (significant on all days), eosinopenia (significant on days 1, 2 and 3) and monocytosis (significant on days 5, 7, 10 and 13).

Table 4 Patient demographics and clinical outcome

No. of patients	61
Age (years)*	28·1(0·5)
Sex	
M	56
F	5
Blunt trauma†	56 (96)
Admissions to ICU†	49 (80)
Haemoperitoneum†	22 (36)
Injury Severity Score*	29·4(0·4)
Uneventful course (n = 55)	27·4(0·4)
Sepsis syndrome (n = 6)	37·2(1·6)
Blood transfusion (units)	
0	9
1–5	31
>5	21
Surgery†	51 (83)
Hospital stay (days)*	34(3)
ICU stay (days)*	10(2)

*Values are mean(s.e.m.). †Values in parentheses are percentages. ICU, intensive care unit

Lymphocyte subset analysis

CD3+ (T-αβ) and γδ+ T cells were diminished throughout the study. Values were lowest between days 1 and 3, and then began to return towards the normal range. CD4+ cells (Th cells) and CD8+ cells (T suppressor/cytotoxic cells) displayed a pattern similar to that of CD3+ cells, with the lowest values being observed on days 2 and 3, followed by a gradual recovery towards normal. CD4+ cells normalized by day 7; CD8+ cells, however, showed a variable pattern with a normal value on day 7 and then low values on days 10 and 13. The more rapid CD4 recovery resulted in a raised CD4 : CD8 ratio after day 2. CD4+ CD45RA+ (naive T), CD45+ CD45RO+ (memory T) and CD4+ CD62+(Leu8+) (naive and memory T subset) cell subsets followed nearly identical patterns. Values were significantly decreased until day 5, with the lowest values on days 2–3.

Mature and immature B lymphocytes (CD20+ and CD20+ CD38+ respectively) remained normal except for a high value on day 7. All natural killer (NK) cell subsets were significantly reduced throughout the study. Like other subsets, a nadir occurred on days 2 or 3, followed by a gradual return towards control values. There were no correlations between any lymphocyte phenotype and clinical outcome.

T lymphocyte surface membrane activation markers

The absolute number of T lymphocytes expressing cell surface activation markers demonstrated two response patterns. CD3+ CD69+ and CD3+ CD25+ cells were within control values on days 1, 2 and 3, and then increased significantly on day 5 (*Figs 1* and *2*). The values remained raised but plateaued on days 7, 10 and 13. CD3+ CD71+ cells were significantly increased on all days (*Fig. 3*). The second pattern (data not shown), observed in CD3+ CD38+ and CD3+ HLA (human leucocyte antigen)-DR+ cells, consisted of reduced values between days 1 and 5, followed by a gradual recovery to normal on day 7. CD3+ VLA(very late activation antigen)+ values were similar to those in controls on all days.

Cytokines and soluble cell surface proteins

Levels of sIL-2R and sCD4 differentiated between patients with an uneventful course and those with sepsis syndrome (*Figs 4* and *5*). The sIL-2R level was significantly increased in all patients on all days; in patients developing sepsis syndrome, values on days 5, 7, 10 and 13 were significantly higher than those in patients with an uneventful recovery. A similar pattern was observed for sCD4; significant differences between the two groups of patients were observed on days 3, 5, 7 and 10. There were modest but significant increases in IL-2 on all days and in soluble CD8 (sCD8) on days 3, 5, 7 and 13 (*Fig. 6*). Serum levels of IFN-γ and IL-4 were not significant.

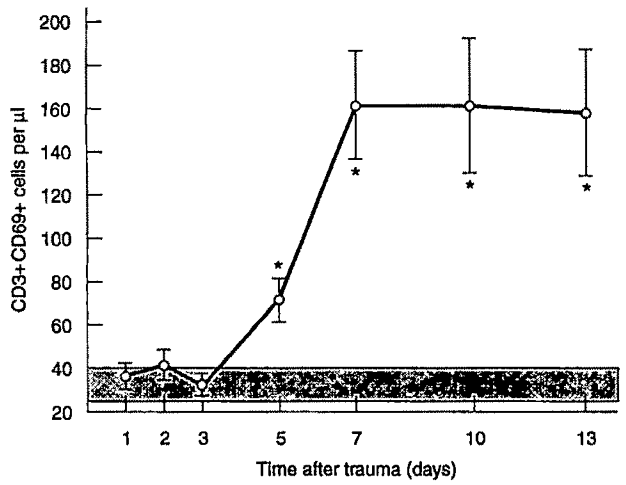

Fig. 1 Mean(s.e.m.) number of CD3+ CD69+ T cells per microlitre of blood from injured patients. The tinted box shows the 95 per cent confidence interval for normal control values. $^*P < 0.05$ *versus* control (Mann–Whitney *U* test)

Cutaneous delayed-type hypersensitivity

Anergy or severe hyporesponsiveness was noted throughout the study. There was no correlation with clinical outcome.

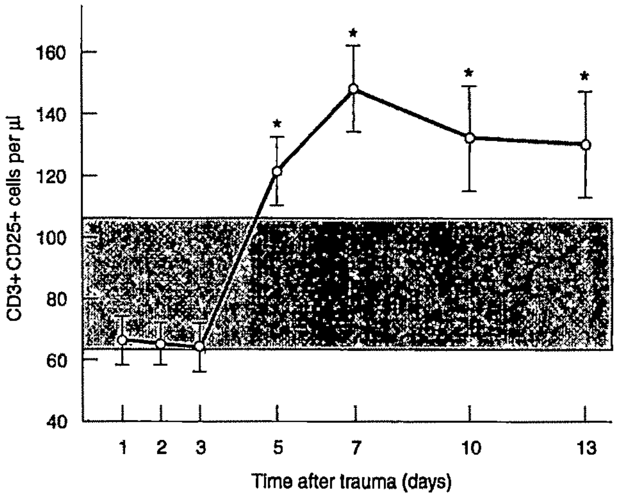

Fig. 2 Mean(s.e.m.) number of CD3+ CD25+ T cells per microlitre of blood from injured patients. The tinted box shows the 95 per cent confidence interval for normal control values. $^*P < 0.05$ *versus* control (Mann–Whitney *U* test)

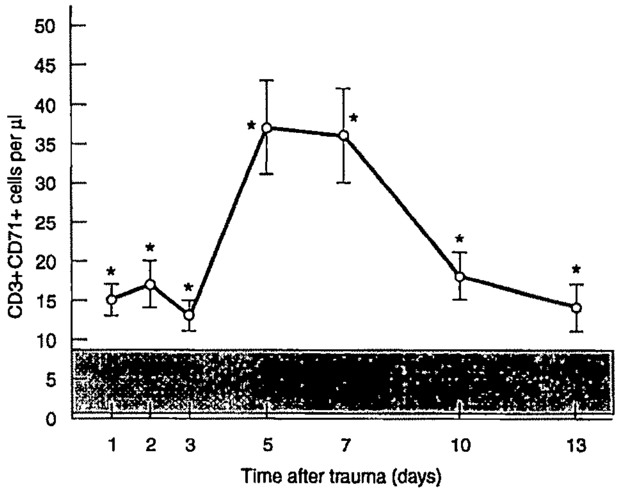

Fig. 3 Mean(s.e.m.) number of CD3+ CD71+ T cells per microlitre of blood from injured patients. The tinted box shows the 95 per cent confidence interval for normal control values. $^*P < 0.05$ *versus* control (Mann–Whitney *U* test)

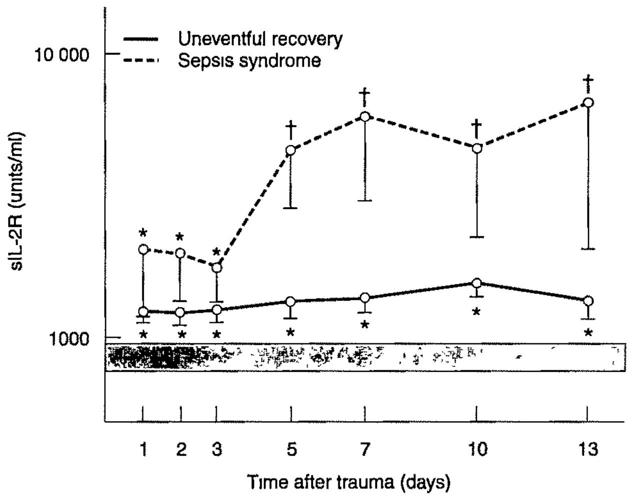

Fig. 4 Mean(s.e.m.) serum level of soluble interleukin 2 receptor (sIL-2R) in injured patients. The tinted box is the 95 per cent confidence interval for normal control values. $^*P < 0.05$ *versus* control, $^†P < 0.05$ *versus* patients with an uneventful recovery (Mann–Whitney *U* test)

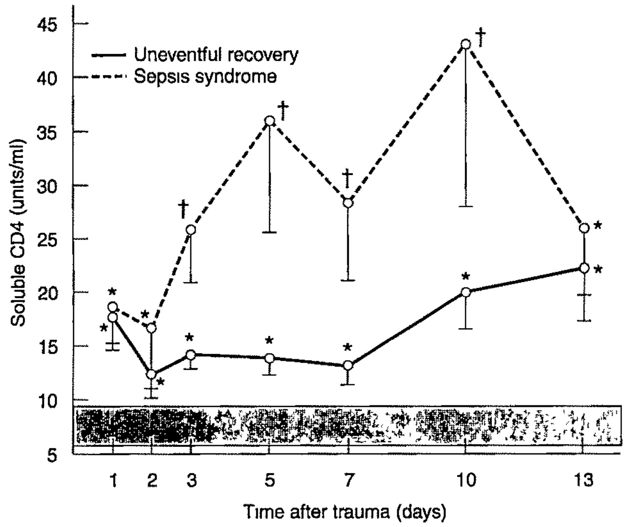

Fig. 5 Mean(s.e.m.) serum level of soluble CD4 in injured patients. The tinted box is the 95 per cent confidence interval for normal control values. $^*P < 0.05$ *versus* control, $^†P < 0.05$ *versus* patients with an uneventful recovery (Mann–Whitney *U* test)

Correlation of immunological measurements with variables other than clinical course

There were no significant relationships between any immunological measurement and the variables described in the demographics (*Table 4*).

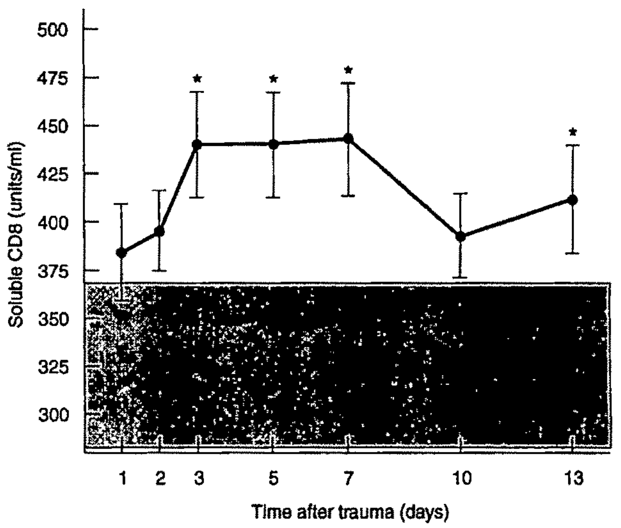

Fig. 6 Mean(s.e.m.) serum level of soluble CD8 in injured patients. The tinted box is the 95 per cent confidence interval for normal control values. $^*P < 0.05$ *versus* control (Mann–Whitney *U* test)

Discussion

It is generally accepted that the SIRS following severe injury generates immunological disturbances that may increase the risk of sepsis[25,26]. Although all immune components are generally affected, especially the monocyte population, lymphocytes are also affected[18,25]. In this study, it was confirmed that non-thermal trauma profoundly affects the numbers of circulating lymphocytes, especially T and NK cells, during the first 3–5 days after injury. It was also shown, for the first time, that $\gamma\delta$+, naive Th and memory Th lymphocytes are also affected. *In vivo* lymphocyte activation was reflected by small but statistically significant increases in the numbers of T cells expressing cell surface markers CD25, CD69 and CD71, and increased serum levels of IL-2, sIL-2R, sCD4 and sCD8. To the authors' knowledge, this is the first description of sCD4 and sCD8 levels in patients with polytrauma.

A consistent observation in many lymphocyte and soluble factor values was a 'pivot' period on day 3 or 5 in which most values began to return to normal. The temporal relevance of the pivot period is unclear, but may be related to tapering levels of corticosteroids or catecholamines, potent mediators of leucocyte trafficking which are released after injury[31–35]. Speculatively, the pivot period may represent a critical window in which either healing continues or, if the SIRS persists, a heightened risk for sepsis[26]. Indeed, in patients who developed serious complications, significantly higher levels of sIL-2R, sCD4 and sCD8 frequently appeared within the pivot period (by day 3 or 5) and, in some cases, correlated with the onset of infectious complications. Further studies in larger numbers of patients may be warranted to define better the prognostic value of these soluble factors.

Increased numbers of T cells expressing CD69, CD25 and CD71, and increased serum levels of IL-2, sIL-2R, sCD4 and sCD8, are consistent with lymphocyte activation[10,11,13,36–38]. Interestingly, increases in the number of T cells expressing CD69 and CD25, which are 'early' and 'mid-range' markers of activation respectively, occurred simultaneously after day 3 in a manner opposite to the pivot observed for most other markers. Increased numbers of CD3+ CD69+ and CD3+ CD25+ T cells detected into the second week suggested a lingering source of activation, perhaps related to the SIRS. Indeed, increased numbers of CD3+ CD69+ T cells for up to 2 weeks was noteworthy because this marker downregulates several hours after expression[39–41], suggesting that new populations of T cells were activating. In contrast, T cells expressing the 'late' activation markers HLA-DR and CD38 remained below or within control values. A pivot event was also seen in levels of sIL-2R and sCD4, particularly in patients with sepsis syndrome after day 3. Because only a few patients developed sepsis syndrome, it remains unclear whether these markers have predictive value. Other cellular or soluble parameters measured did not discriminate between an uneventful course and sepsis syndrome.

These data are in agreement with previous reports describing *in vivo* lymphocyte activation following severe injury, especially burns[10,11,13,15–17,38], and may be useful in understanding the discord between lymphocyte *in vitro* deficiencies and *in vivo* activation. Indeed, Xu *et al.*[15] found that scrupulously isolated peripheral blood mononuclear cells from polytrauma patient samples respond normally to mitogen stimulation and, more recently, De *et al.*[42] showed that only a minority develop actual T lymphocyte deficiencies. Rather, trauma may induce a polarized T cell response in which high levels of the Th2-like cytokines IL-10 and IL-4 are produced[19,21–24,43]. A polarized T cell response may result from prostaglandin E_2, a potent eicosanoid released from monocytes after severe injury which induces IL-10 and IL-4 production, and inhibits IL-2 and IFN-γ production[43,44]. A predominant Th2-like response could account for *in vitro* observations such as spontaneous lymphocyte blastogenesis or functional T lymphocyte deficiencies such as reduced IL-2 and IFN-γ production after mitogen stimulation, as well as *in vivo* polyclonal B cell proliferation, skin test anergy and perhaps increased susceptibility to sepsis[4,5,9,12,16–18,21,25,43,45]. Indeed, skin testing is a highly reliable indicator of cell-mediated immune function which requires a robust Th1-like response with abundant IL-2 production. As in other series[8,9], skin test anergy was observed in nearly all of the present patients, regardless of clinical course.

The clinical significance of lymphocyte activation after trauma remains unclear. Some argue that lymphocyte alterations after trauma are not necessarily detrimental but rather physiological responses that occur after any severe stress[35]. The present data, together with reports describing polarized T cell responses, provide new insights into the sequence of immunological events after injury. Although biological variation may indeed be a factor in patient recovery from trauma[27] which supercedes any measurable physiological change, a panel of soluble factors (including inflammatory factors) and cell surface markers that correlate with clinical course might still be a useful tool for identifying patients at high risk of sepsis. To that end, further investigation is clearly warranted.

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Original article

Acrylate yellow filters in operating lights protect against photosensitization tissue damage

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Background: Photosensitized patients are exposed to bright lights when undergoing intraoperative photodynamic therapy or fluorescence measurements. Acrylate yellow filters might reduce unwanted tissue damage.

Methods: To investigate the protective value of these filters, the spectral power distribution of the operating lights and light energy densities with and without an acrylate yellow filter were measured. Subsequently the effects of light exposure on the survival of a human hepatocellular carcinoma cell line and the photodamage induced in pig tissues after the administration of 5-aminolaevulinic acid were also studied.

Results: The light energy density in the ultraviolet and blue region of the light spectrum emitted by the operating light was reduced up to 50 per cent by the acrylate yellow filter. The survival of photosensitized cells was longer and photodamage induced in pig tissues was less when exposed to filtered light.

Conclusion: Photodamage induced by operating lights can be reduced by filtering out ultraviolet and blue light by means of acrylate yellow filters.

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Introduction

Photodynamic therapy (PDT) has been proposed as an adjuvant to cancer surgery to reduce local recurrence. PDT during operation is complicated by the fact that photosensitized patients are exposed to operating lights in addition to the light source used for PDT[1–3]. The protoporphyrin IX (PPIX) precursor 5-aminolaevulinic acid (ALA) is currently under study as a potential photosensitizer for gastrointestinal cancer[4]. PPIX is formed by both tumour and normal tissues, and normal organs are also vulnerable if exposed to light of a broad spectrum during the period of PPIX accumulation[5,6].

This investigation aimed to determine whether the use of acrylate yellow filters, which filter out the shorter wavelengths of the spectrum of the operating lights (ultraviolet (UV) and blue region), might reduce tissue damage. Others have also used these filters as a safety measure when operating on photosensitized patients, but their protective value does not appear to have been studied[7–9].

First, the survival of a human hepatoma cell line, HepG2, was studied after incubation with ALA and subsequent exposure to operating lights with and without an acrylate yellow filter[10,11]. Second, the effect of acrylate yellow filters on pigs being exposed to an operating light during laparotomy following administration of ALA was determined.

Materials and methods

Light source and acrylate yellow filter

An Angenieux operating light type AX14 (Gambro Medische Apparaten, Breda, The Netherlands) with two halogen bulbs (150 W) was used for the HepG2 cell line study. The spectral power distribution was determined by a MultiSpec 125 spectrometer attached to an InstaSpec IV CCD camera (Oriel Instruments Corporation, Stratford, Connecticut, USA). A Bechtold C-571 operating light (Colombus Medical, Zaltbommel, The Netherlands) with essentially the same spectral power distribution was used for the pig experiments. The acrylate yellow 303 filter (4-mm thickness) was obtained from Wientjes (Roden, The Netherlands) and cut to fit the operating lights.

HepG2 cell line study

HepG2 cells. HepG2 cells were grown as described previously[10], harvested at the moment of exponential growth and seeded in six-well plates at about $0{\cdot}5 \times 10^6$ cells per well.

Porphyrin analysis. Porphyrins were measured by a modification of the method of Chisolm and Brown[12] as described previously[13], and expressed as picomoles per 10^6 cells.

Irradiation. Cells were incubated with or without 0·3 mmol/l ALA for 2 h under conditions described by Vonarx-Coinsman *et al.*[14]. Following incubation, cells were cultured for 3 h without ALA. Subsequently, they were exposed for 0, 5, 10, 15 or 20 min to filtered or unfiltered focused light, at 40 cm. Thereafter, cells were cultured until cell viability was determined by the trypan blue exclusion test at 24 h after irradiation.

Pig experiments

ALA administration. Experiments were performed on two male pigs weighing 21·5 and 22·0 kg. After fasting for 24 h and 12 h without water, the pigs were sedated with 5 ml ketamine intramuscularly (100 mg/ml; Apharmo Holland, Arnhem, The Netherlands). ALA 75 mg/kg (Fluka, Buchs, Switzerland) in 150 ml phosphate-buffered saline was administered by gavage. Blood samples were taken.

Laparotomy and irradiation. Pigs were anaesthetized with 70 per cent nitrous oxide and 30 per cent oxygen, 2 per cent enflurane (Abbott, Amstelveen, The Netherlands), 6 ml fentanyl citrate intravenously (0·05 mg/ml; Janssen–Cilag, Tilburg, The Netherlands) and 2 ml curare intravenously (2 mg/ml; Organon Teknika, Boxtel, The Netherlands). Some 5 h after ALA administration, liver, small intestine and stomach surfaces were exposed to the focused operating light at 80 cm for 30 min. Other organs were covered. One pig was exposed to filtered light, the other to unfiltered light. Light power densities (mW/cm^2) were measured with sterile photodetectors (coherent model 210 and UDT model 81; United Detector Technology, Palo Alto, California, USA). Exposed areas were marked. Dark sides of the organs were used to assess dark toxicity.

Post-mortem examination. Some 48 h after laparotomy, pigs were sedated with 5 ml ketamine (100 mg/ml) and the organs were inspected by the same surgeon. The pigs were then killed and tissue samples were taken.

Histological examination. Tissue samples were fixed with formalin, sectioned, stained with haematoxylin and eosin, and examined.

Laboratory measurements. ALA and porphobilinogen deaminase (PBG) concentrations in plasma were determined using a fluorometric enzyme assay according to a procedure described by de Rooij *et al.*[15]. Levels of alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) in serum were determined (Granutest 25; Merck, Darmstadt, Germany).

Results

Spectral power distribution and acrylate yellow filter characteristics

The maximum light power density of the operating light was 30 mW/cm^2. The spectral power distribution of the operating lights with and without the acrylate yellow filter and the excitation spectrum of PPIX are shown in *Fig. 1*. The filter eliminates nearly all UV and blue light below a wavelength of about 520 nm.

HepG2 cell line study

HepG2 cells accumulated PPIX from exogenous ALA (results not shown). Exposure of cells to filtered light (protected cells) for 5 min resulted in a surviving fraction of 89 per cent 24 h later (*Fig. 2*). Only 39 per cent of the unprotected cells survived. This initial sixfold reduction in cell death decreased after longer exposure times. After 10 min exposure, 35 per cent of protected cells survived, compared with 18 per cent of unprotected cells, and after exposure for 20 min the surviving fractions were 13 and 5 per cent for protected and unprotected groups respectively. At all time points twice as many protected cells survived compared with unprotected cells. Non-irradiated ALA-incubated as well as irradiated non-ALA-incubated cells multiplied throughout the experiment. The temperature of the medium remained constant in all groups.

Pig experiments

ALA plasma concentrations, determined at various intervals, peaked at or before 4 h after ALA administration. At 24 h, ALA was not detectable in plasma.

Light power densities in peripheral fields and in fields directly in focus were measured during laparotomy, and varied from 0·1 to 21 mW/cm^2 without the filter and from 0·1 to 10 mW/cm^2 with the filter. The total light energy densities reaching the liver, small intestine and stomach

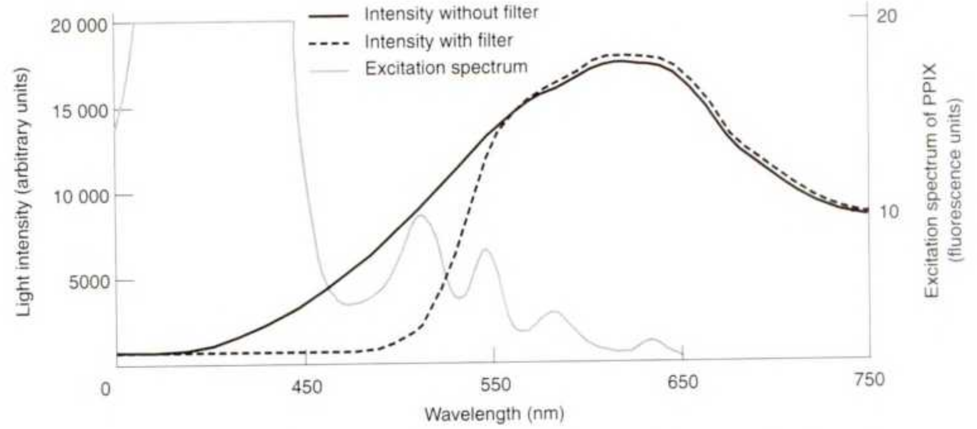

Fig. 1 Spectral power distribution of an operating light with and without an acrylate yellow filter, and the relative excitation spectrum of protoporphyrin IX (PPIX)

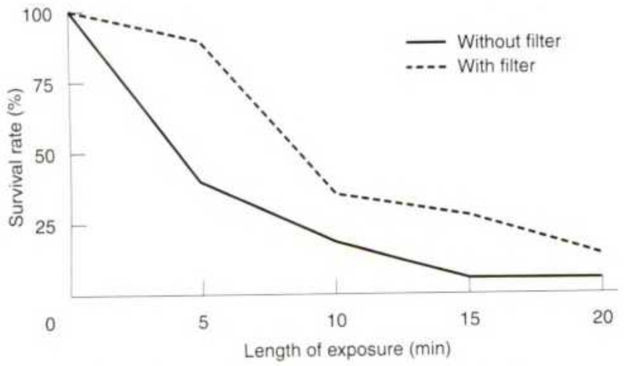

Fig. 2 Survival of photosensitized HepG2 cells 24 h after 0, 5, 10, 15 and 20 min of exposure to an operating light with and without an acrylate yellow filter

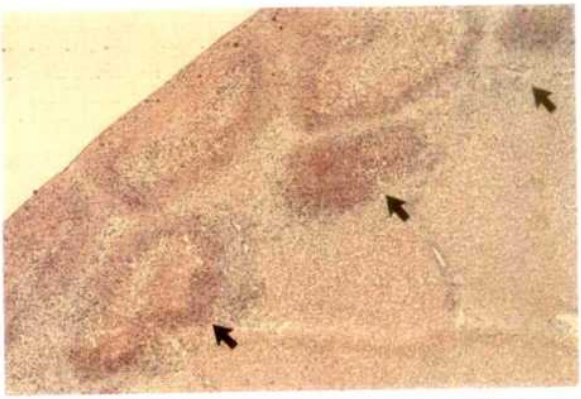

Fig. 3 Necrotic zone (1 mm) at the illuminated site of the liver surface without the filter. Arrows point towards the liver surface and demarcate the necrotic zone (original magnification × 20)

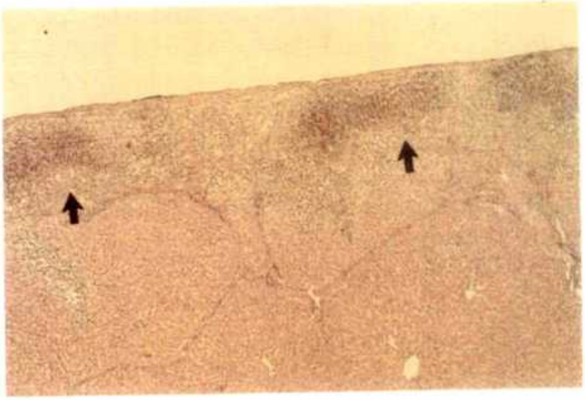

Fig. 4 Necrotic zone (0·5 mm) at the illuminated site of the liver surface with the filter. Arrows point towards the liver surface and demarcate the necrotic zone (original magnification × 20)

surfaces consisted of direct (focused) illumination for 30 min and indirect illumination (preparation time and peripheral light during exposure of other organ) for 75 min. Some 66–70 J/cm^2 reached the organs without the filter and 34–36 J/cm^2 reached the organs with a filter. Therefore, a 50 per cent reduction of total light energy density, mainly of UV and blue light (wavelength less than 520 nm; *Fig. 1*), was caused by the filter.

During exposure to unfiltered light, macroscopic changes included redness of the gastric serosa, a white contracting serosa of the small intestine, a colour change of the liver from brown to yellow, and a change to a wrinkled aspect of the liver surface. These changes were less pronounced after exposure to filtered light.

At post-mortem examination, macroscopic changes after illumination without the filter were more pronounced. Haemorrhagic spots existed and the tissue was swollen compared with the dark control side of the same organ or tissue illuminated using the filter.

Histologically, no changes were found in the dark control tissues of both pigs. There were clear differences in liver histology between areas illuminated with or without the filter (*Figs 3* and *4*). Liver necrosis was twice as deep when the filter was not used (1·0 *versus* 0·5 mm). Necrosis was not seen in the stomach and small intestine, but oedema, leucocyte infiltration and disintegration of muscle cells were observed. Transient (for 48 h) increases in ASAT concentration were more pronounced in the pig operated on without the filter. There was no skin damage or abnormal behaviour.

Discussion

PPIX is highly photosensitizing, as shown in the disease erythropoietic protoporphyria. Photochemical reactions are induced by UV and blue light[16]. It seems reasonable to protect patients undergoing surgery who have been photosensitized after ALA administration, by using filters that block UV and blue light.

Acrylate yellow filters, which cut off wavelengths shorter than 520 nm, reduce the light energy density by 50 per cent, mainly in the UV and blue light range (*Fig. 1*). These filters were found to protect photosensitized HepG2 cells when exposed to operating lights for less than 5 min. With an exposure time exceeding 5 min, the filter failed to prevent cell death. However, even after longer exposure, the survival rate of cells protected by the filter during irradiation was still twice as high as that of cells irradiated without a filter. Acrylate yellow filters also had a protective effect in pigs after ALA pretreatment. Both macroscopic and microscopic damage was less pronounced when the light was filtered. Energy densities in these experiments were higher than the known energy densities provided to human tissues during operation, as measured by Allardice *et al.*[17]. These authors studied the safety of intraoperative PDT with haematoporphyrin derivative; however, they defocused the operating lights at 1·30 m from the investigated area, creating minimum illuminance. Allardice and co-workers concluded that operating lights can reach unacceptably high energy levels and that an additive dose given by intraoperative PDT might cause unwanted side-effects. They mentioned the possible use of yellow filters but concluded that yellow light may be unacceptable to surgeons.

The present study demonstrates that acrylate yellow filters have a protective effect. However, after longer exposure to filtered light, tissue damage is likely to occur and surgeons should probably still cover organs that are not in the immediate operating field to prevent unnecessary light exposure and damage. Some anatomical structures (e.g. ureters and hypogastric nerves) might have their colour appearance changed and surgeons should be aware that a colour change may hinder their recognition of structures. Meerman *et al.*[7] used acrylate yellow filters during liver transplantation in patients suffering from erythropoietic protoporphyria. The abnormal colour perception did not hamper the surgeons and other personnel.

In the present authors' hospital, these filters were used in ten photosensitized patients during resection and reconstruction of the oesophagus. There was no deterioration in the visibility of structures and the use of these filters was fully acceptable to the surgeons. Surrounding lights in the operating theatre do not add much to the light energy density reaching the exposed organs (results not shown), so these lights can be kept on for the convenience of the nursing and anaesthetic personnel.

In conclusion, the use of acrylate yellow filters is recommended when photosensitized patients are operated on, and also when porphyrin concentrations are to be measured in tissue obtained at operation, to minimize photoactivation.

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Original article

Recurrence following curative resection for gastric carcinoma

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Background: The diagnosis and treatment of recurrent gastric cancer remains difficult. The aim of this study was to determine the risk factors for recurrence of gastric cancer and the prognosis for these patients.

Methods: Of 2328 patients who underwent curative resection for gastric cancer from 1987 to 1995, 508 whose recurrence was confirmed by clinical examination or reoperation were studied retrospectively. The risk factors that determined the recurrence patterns and timing were investigated by univariate and multivariate analysis.

Results: The mean time to recurrence was 21·8 months and peritoneal recurrence was the most frequent (45·9 per cent). Logistic regression analysis showed that serosal invasion and lymph node metastasis were risk factors for all recurrence patterns and early recurrence (at 24 months or less). In addition, independent risk factors involved in each recurrence pattern included younger age, infiltrative or diffuse type, undifferentiated tumour and total gastrectomy for peritoneal recurrence; older age and larger tumour size for disseminated, haematogenous recurrence; and older age, larger tumour size, infiltrative or diffuse type, proximally located tumour and subtotal gastrectomy for locoregional recurrence. Other risk factors for early recurrence were infiltrative or diffuse type and total gastrectomy. Reoperation for cure was possible in only 19 patients and the mean survival time after conservative treatment or palliative operation was less than 12 months.

Conclusion: The risk factors for each recurrence pattern and timing of gastric cancer can be predicted by the clinicopathological features of the primary tumour. Since the results of treatment remain dismal, studies of perioperative adjuvant therapy in an attempt to reduce recurrence are warranted.

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Introduction

Gastric cancer is still the most common cause of death from cancer in Korea, despite improved prognosis as a result of early diagnosis, radical operations and the development of adjuvant therapy[1–3]. Death from gastric cancer is almost entirely due to recurrent disease, and recurrences are often found in various forms or at more than one site simultaneously. Therefore, it is difficult clinically to confirm the patterns of recurrence and to establish precise data about the relationship between patterns of recurrence and the therapeutic strategy in gastric cancer. However, clarifying the relationship between clinicopathological factors and patterns of recurrence may contribute to the choice of better treatment or follow-up programme.

This study reviewed experience with recurrent gastric cancer after curative resection and evaluated the following: (1) patterns and timing of recurrence, (2) risk factors according to patterns of recurrence, and (3) prognosis according to patterns of recurrence and mode of treatment.

Patients and methods

The records of 2328 consecutive patients who underwent potentially curative resection for gastric cancer from January 1987 to June 1995 were reviewed. All patients had histologically confirmed adenocarcinoma of the stomach without clinical or radiological evidence of distant metastases. At operation, either total or distal subtotal gastrectomy was performed depending on location and macroscopic type of gastric cancer. All patients underwent extended lymphadenectomy, and a minimum of 15 lymph nodes was retrieved. The cancer was staged according to the Union Internacional Contra la Cancrum (UICC) tumour node metastasis (TNM) classification[4].

The patients were followed closely until 31 December 1998; the median length of follow-up was 68 (range

1–144) months. Routine follow-up consisted of physical examination, laboratory tests (including estimation of carcinoembryonic antigen, CA19-9 and CA125 levels), chest radiography, abdominopelvic ultrasonography and computed tomography (CT). However, follow-up intervals were individualized according to the TNM stage of each patient. In early stages (stage IA or IB), patients were followed every 4 months during the first 2 years, and then every 6 months or yearly beyond the third year; in advanced stages (stage II or greater), follow-up was every 3 months during the first year, every 4 months during the second, and every 6 months thereafter, for a total of 5 years. Endoscopy was performed every 6 months or yearly, and other radiological studies were performed only on suspicion of recurrence.

At the time of the last follow-up, 1499 patients (64·4 per cent) were still alive, 72 (3·1 per cent) were lost to follow-up and 757 (32·5 per cent) had died from recurrence or other causes. Of 652 patients (28·0 per cent) with recurrent gastric cancer, the exact sites of failure were unknown due to incomplete data in 144.

Therefore, 508 patients whose recurrence was confirmed by clinical and radiological examination ($n = 411$) or by reoperation ($n = 97$) were entered in the study. Of these patients, recurrent cancer was pathologically proven in 197 patients (38·8 per cent).

The main patterns of recurrence were recorded as the first site of detectable failure at the time of diagnosis, and patients were divided into three groups: locoregional, peritoneal and haematogenous (disseminated) recurrence. The criteria and the number of patients according to each recurrence pattern are shown in *Table 1*. Lymph nodes included the regional nodes (perigastric, left gastric, common hepatic, coeliac and hepatoduodenal lymph nodes) as well as retropancreatic, mesenteric and para-aortic nodes. The determination of locoregional recurrence was made by endoscopy, ultrasonography, CT or reoperation. Peritoneal recurrence was determined by ultrasonography, CT, barium enema, intravenous pyelography and reoperation, as well as the appearance of clinical signs such as ascites, rectal shelf, intra-abdominal mass, abdominal wound or drain site mass, intractable intestinal obstruction or obstructive uropathy. Haematogenous recurrence was determined by chest radiography, ultrasonography, CT, scintigraphy or pathological diagnosis.

Table 1 Patterns of recurrence in gastric cancer

	Alone	Combined
Locoregional	98 (19·3)	165 (32·5)
Anastomosis or stump	54 (10·6)	80 (15·7)
Lymph nodes	34 (6·7)	68 (13·4)
Adjacent organ	10 (2·0)	13 (2·6)
Peritoneal	172 (33·9)	223 (43·9)
Haematogenous	133 (26·2)	174 (34·3)
Liver	75 (14·8)	96 (18·9)
Lung	26 (5·1)	35 (6·9)
Bone	26 (5·1)	34 (6·7)
Brain	5 (1·0)	8 (1·6)
Testis	1 (0·2)	1 (0·2)
Extra-abdominal nodes*	22 (4·3)	24 (4·7)

Values in parentheses are percentages. *Supraclavicular, inguinal or axillary lymph nodes

Statistical analysis

The relationships between the recurrence patterns and variable clinicopathological factors were compared, with special reference to the length of time to recurrence and the prognosis. Statistically significant differences were analysed with the two-tailed χ^2 test and Student's t test. The risk factors that influence patterns and timing of recurrence were determined by means of logistic regression analysis. Forward stepwise selection with a likelihood ratio test was used for selecting variables. The odds ratio (OR) in logistic regression analysis was defined as the ratio of the probability that an event will occur to the probability that it will not occur.

The prognostic power of covariates was expressed by calculation of a relative risk or OR with 95 per cent confidence intervals. $P < 0{\cdot}05$ was considered statistically significant. All statistical analyses were carried out with the SPSS for Windows (SPSS, Chicago, Illinois, USA) program.

Results

Patterns of recurrence

The main patterns of recurrence in 508 patients are shown in *Fig. 1*. Of these, 403 patients had only one recurrence pattern and 83 (16·3 per cent) had two or more sites of recurrence at the time of diagnosis. As a single pattern, peritoneal recurrence (33·9 per cent) was observed most frequently, followed by haematogenous (26·2 per cent) and locoregional (19·3 per cent) recurrence. The most common combined pattern was locoregional recurrence with peritoneal recurrence in 42 patients (8·3 per cent). Extra-abdominal lymph node metastases such as supraclavicular, inguinal or axillary nodes were found in 22 patients (4·3 per cent). As shown in *Table 1*, the highest incidence of locoregional recurrence was in the anastomosis or stump in 80 patients (15·7 per cent), followed by lymph nodes in 68 patients (13·4 per cent). The most common site of

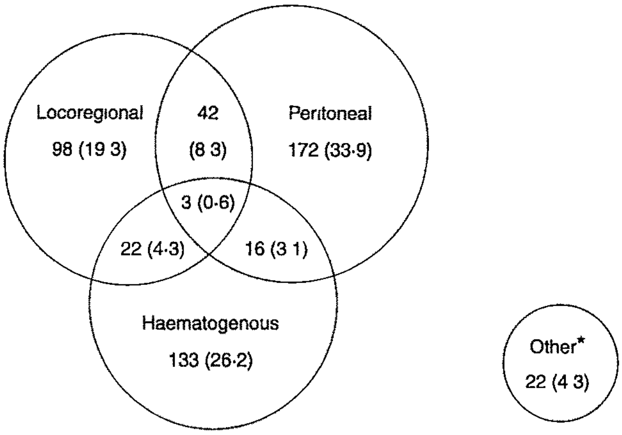

Fig. 1 Patterns of recurrence in 508 patients after curative resection. Values in parentheses are percentages. *Recurrence at the extra-abdominal lymph nodes

haematogenous recurrence was the liver, occurring in 96 patients (18·9 per cent) and in 75 (14·8 per cent) as the only site of recurrence. The relationship between the clinicopathological features of patients and the single pattern of recurrence is shown in *Table 2*. Age, gross and histological type of tumour, and depth of invasion were significantly different between the main patterns of recurrence ($P < 0·001$).

Length of time to recurrence

The mean length of time to recurrence was 21·8 (range 3–120) months. For each recurrence pattern, the mean time was 27·3 months for locoregional recurrence, 18·1 months for peritoneal recurrence and 14·6 months for haematogenous recurrence ($P < 0·001$, Student's t test).

The patients were divided into an early recurrence group (24 months or less) and a late recurrence group (more than

Table 2 Clinicopathological features according to single recurrence patterns

	Locoregional (n=98)	Peritoneal (n=172)	Haematogenous (n=133)	P^*
Sex				0·24
M	65 (66·3)	108 (62·8)	92 (69·2)	
F	33 (33·7)	64 (37·2)	41 (30·8)	
Mean age (years)	56·8	50·3	55·9	< 0·001
Tumour size (cm)				0·68
≤ 4	35 (35·7)	54 (31·4)	46 (34·6)	
> 4	63 (64·3)	118 (68·6)	87 (65·4)	
Tumour location				0·37
Upper third	17 (17·3)	21 (12·2)	20 (15·0)	
Middle third	40 (40·8)	58 (33·7)	50 (37·6)	
Lower third	36 (36·7)	81 (47·1)	60 (45·1)	
Whole	5 (5·1)	12 (7·0)	3 (2·3)	
Gross type				< 0·001
Superficial	5 (5·1)	1 (0·6)	12 (9·0)	
Localized	21 (21·4)	16 (9·3)	30 (22·6)	
Infiltrative or diffuse	72 (73·5)	155 (90·1)	91 (68·4)	
Histological type				< 0·001
Differentiated	28 (28·6)	32 (18·6)	58 (43·6)	
Undifferentiated	70 (71·4)	140 (81·4)	75 (56·4)	
Depth of invasion				< 0·001
pT_1	5 (5·1)	1 (0·6)	12 (9·0)	
pT_2	24 (24·5)	16 (9·3)	27 (20·3)	
pT_3	65 (66·3)	144 (83·7)	88 (66·2)	
pT_4	4 (4·1)	11 (6·4)	6 (4·5)	
Lymph node metastasis				0·24
pN_0	21 (21·4)	27 (15·7)	26 (19·5)	
pN_1	33 (33·7)	60 (34·9)	44 (33·1)	
pN_2	31 (31·6)	53 (30·8)	33 (24·8)	
pN_3	13 (13·3)	32 (18·6)	30 (22·6)	
Type of resection				0·06
Subtotal	69 (70·4)	96 (55·8)	83 (62·4)	
Total	29 (29·6)	76 (44·2)	50 (37·6)	

Values in parentheses are percentages. pT, pathological tumour, pN, pathological node (classification). $^*\chi^2$ or Student's t test

Table 3 Clinicopathological features according to recurrence time

	Early recurrence ($\leq$ 24 months) (n = 368)	Late recurrence (> 24 months) (n = 140)	P*
Sex			0·19
M	251 (68·2)	87 (62·1)	
F	117 (31·8)	53 (37·9)	
Mean age (years)	54·3	52·1	0·17
Tumour size (cm)			0·10
$\leq$ 4	119 (32·3)	56 (40·0)	
> 4	249 (67·7)	84 (60·0)	
Tumour location			0·052
Upper third	54 (14·7)	16 (11·4)	
Middle third	141 (38·3)	40 (28·6)	
Lower third	155 (42·1)	78 (55·7)	
Whole	18 (4·9)	6 (4·3)	
Gross type			< 0·001
Superficial	10 (2·7)	16 (11·4)	
Localized	62 (16·8)	20 (14·3)	
Infiltrative or diffuse	296 (80·4)	104 (74·3)	
Histological type			0·013
Differentiated	115 (31·2)	28 (20·0)	
Undifferentiated	253 (68·8)	112 (80·0)	
Depth of invasion			< 0·001
pT$_1$	10 (2·7)	16 (11·4)	
pT$_2$	50 (13·6)	33 (23·6)	
pT$_3$	287 (78·0)	85 (60·7)	
pT$_4$	21 (5·7)	6 (4·3)	
Lymph node metastasis			< 0·001
pN$_0$	50 (13·6)	43 (30·7)	
pN$_1$	115 (31·2)	53 (37·8)	
pN$_2$	118 (32·1)	33 (23·6)	
pN$_3$	85 (23·1)	11 (7·9)	
Type of resection			< 0·001
Subtotal	215 (58·4)	106 (75·7)	
Total	153 (41·6)	34 (24·3)	

Values in parentheses are percentages. pT, pathological tumour, pN, pathological node (classification). *χ^2 or Student's t test

24 months) for correlation with clinicopathological features (*Table 3*). In the early recurrence group, patients with infiltrative or diffuse type of cancer, differentiated tumour, serosal invasion, lymph node metastasis, and who had undergone total gastrectomy were common in comparison with the late recurrence group ($P < 0·05$).

Multivariate analysis of risk factors

The independent risk factors involved in the recurrence of gastric cancer were, in order: lymph node metastasis, serosal invasion, infiltrative or diffuse type, larger tumour size (4 cm or greater), undifferentiated tumour and proximally located tumour (*Table 4*). A further multivariate analysis according to the recurrence patterns (*Fig. 2*) showed that serosal invasion and lymph node metastasis were common risk factors for all recurrence patterns. In addition, peritoneal recurrence was closely related to younger age (50 years or less), infiltrative or diffuse type, undifferentiated tumour and total gastrectomy; haematogenous recurrence was related to older age (above 50 years) and larger tumour size; while locoregional recurrence was related to older age, larger tumour size, infiltrative or diffuse type, proximally located tumour and subtotal gastrectomy. The independent risk factors for early recurrence of gastric cancer were lymph node metastasis (OR 4·988), serosal invasion (OR 3·104), infiltrative or diffuse type (OR 1·890) and total gastrectomy (OR 1·534).

Survival after recurrence

Of 508 patients, 481 died and 27 were still alive after diagnosis of recurrence. Of these 27 patients, only five were disease-free after curative reoperation; the remaining 22 are still alive with recurrent disease. Most patients died within the first year after diagnosis of recurrence and the mean survival time was 8·7 (range 2–66) months. According to the recurrence patterns, patients with peritoneal recurrence

Table 4 Logistic regression analysis of independent risk factors for recurrence of gastric cancer

	β	Odds ratio	P*
Age ($\leq$ 50 years, > 50 years)	0·044	1·046 (0·868–1·258)	0·636
Sex (M, F)	0·056	1·057 (0·825–1·354)	0·659
Tumour size ($\leq$ 4 cm, > 4 cm)	0·411	1·507 (1·174–1·934)	0·001
Tumour location (distal, proximal)	0·199	1·220 (1·006–1·481)	0·043
Gross type (superficial or localized, infiltrative or diffuse)	0·592	1·808 (1·483–2·205)	< 0·001
Histological type (differentiated, undifferentiated)	0·328	1·387 (1·072–1·795)	0·012
Serosal invasion (none, present)	0·887	2·428 (1·825–3·229)	< 0·001
Nodal metastasis (none, present)	1·345	3·838 (2·926–5·036)	< 0·001
Type of resection (subtotal, total)	0·142	1.153 (0·813–1·634)	0·423
Lymph node dissection (D$_2$, D$_3$ or more)	−0·113	0·893 (0·759–1·051)	0·173

Values in parentheses are 95 per cent confidence intervals. Dependent variables (no recurrence, recurrence) *Likelihood ratio test

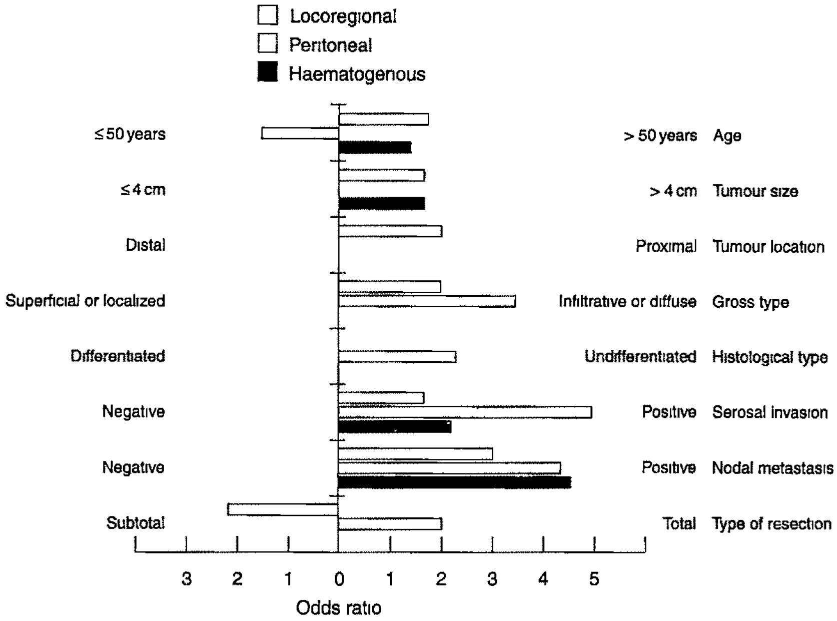

Fig. 2 Independent risk factors according to recurrent pattern by logistic regression analysis ($P < 0.05$)

Table 5 Treatment for recurrent gastric cancer and mean survival time related to treatment

Type of treatment	No. of patients	Mean survival (months)
Conservative treatment*	411 (80·9)	8·3
Laparotomy only	25 (4·9)	6·7
Bypass procedure	24 (4·7)	8·5
Palliative resection	29 (5·7)	11·6
Curative resection	19 (3·7)	21·6

Values in parentheses are percentages. *With or without chemotherapy or radiation therapy

died most quickly (mean 6·4 months), followed by those with haematogenous (9·4 months) and locoregional (11·0 months) recurrence. Nineteen patients in whom curative resection was possible survived the longest, with a mean of 21·6 months. However, the mean survival time after non-curative or palliative surgery was less than 12 months (*Table 5*).

Discussion

The disagreement in the literature on recurrence patterns is probably related to the patient cohorts undergoing evaluation, the time at which recurrence was determined, and the methods for determining recurrence patterns. There have been many studies based on autopsy findings, but autopsies reveal only the end patterns of failure[5–7]. Gunderson and Sosin[8] reported a reanalysis of the reoperation series performed by Wangensteen *et al.*[9] at the University of Minnesota, in which patients had a second-look laparotomy after resection of the primary tumour. This type of analysis might be valuable because it can demonstrate the early modes of recurrence rather than simply showing diffuse metastatic disease at autopsy. However, routine second-look surgery has not proven to be a worthwhile procedure in gastric cancer because it can allow for an earlier diagnosis but does not improve the patient's prospects of recovery following treatment[10,11].

In this study, the recurrence patterns were based on clinical or radiological examination, and there may be some underestimation of the exact sites of recurrence. However, the results confirmed that recurrence after curative resection for gastric cancer occurred mostly within the first 2 years after operation in patients with an advanced stage of gastric cancer. Only 26 patients (5·1 per cent) had documented recurrence from early gastric cancer, and the recurrence patterns were haematogenous recurrence ($n = 12$), locoregional recurrence ($n = 5$), peritoneal recurrence ($n = 1$), or a combined pattern ($n = 8$). This study also demonstrated that intra-abdominal spread of the tumour (locoregional, liver or peritoneal recurrence) was the major feature of both single and multicomponent recurrence. Extra-abdominal, haematogenous or lymphatic spread without intra-abdominal metastases occurred rarely.

In two autopsy studies, the rate of locoregional recurrence following potentially curative resection was 40–80 per cent[6,12], but more recent series have suggested a higher incidence of peritoneal recurrence; Japanese researchers have reported that peritoneal surfaces and the liver were the major sites of treatment failure after D_2 or D_3 resection[13,14].

The present study also found that the incidence of locoregional recurrence was the lowest among the recurrence patterns. The site most prone to locoregional recurrence was the anastomosis or stump (15·7 per cent) following distal subtotal ($n = 70$) or total ($n = 10$) gastrectomy; the next was the lymph nodes (13·4 per cent), mostly at the mesenteric or para-aortic nodes rather than the regional lymph nodes. This may be due to routine D_2 or D_3 lymph node dissection. It is therefore possible that extended lymphadenectomy with intraoperative frozen-section examination of the resection margins may further decrease the incidence of locoregional recurrence in gastric cancer after curative resection.

There have been several studies of the relationship between recurrence patterns, time to recurrence and clinicopathological features[15–21]. Borrmann type III or IV, poorly differentiated tumours, as well as tumours with serosal invasion, adjacent tissue invasion or free intraperitoneal cancer cells, have been reported to be associated with a high risk of subsequent peritoneal spread[17–20]. It has also been reported that haematogenous recurrence, in particular liver recurrence, develops more frequently from Borrmann type I or II and well differentiated tumours[21], so that the incidence of haematogenous recurrence is relatively higher in cases of early gastric cancer[22,23].

From the logistic regression analysis, serosal invasion and lymph node metastasis were common risk factors for all recurrence patterns: serosal invasion was the highest risk factor for peritoneal recurrence, and lymph node metastasis for haematogenous recurrence. It was noteworthy that age was a different risk factor according to the recurrence pattern: younger age was a risk factor for peritoneal recurrence, whereas older age was a risk factor for haematogenous and locoregional recurrence. Differentiated tumour was predominant in haematogenous recurrence, but was not an independent risk factor for this type of recurrence in the multivariate analysis.

Furthermore, lymph node metastasis was the most significant risk factor for recurrence of gastric cancer, as well as the early recurrence of tumour. Recent studies[24,25] have disclosed that the number of metastatic lymph nodes is an important prognostic factor in gastric cancer. Siewert *et al.*[26] also reported that lymph node ratio and residual tumour are the major independent prognostic factors in patients with resected gastric cancer, and that extended lymph node dissection is the most important factor determining long-term survival in patients with stage II gastric cancer.

A number of factors, including a low rate of resectability, poor patient tolerance for treatment, frequent postoperative morbidity and mortality after operation, and an overall dismal prognosis, lead to pessimism when faced with recurrent gastric cancer[27]. The prognosis of recurrent gastric cancer in the present series was generally poor with a mean survival time of 8·7 months. Patients with peritoneal or haematogenous recurrence mostly died within 10 months after diagnosis of recurrence. Furthermore, the proportion of operations for recurrence and the prospects of a secondary cure were extremely limited. Of 508 patients, curative resection of locoregionally recurrent cancer was possible in only 19 patients (3·7 per cent), and only five patients (1·0 per cent) remained disease-free. Removal of metastatic tumour at the abdominal wound, drain site, extra-abdominal lymph nodes, or in the peritoneal cavity with or without adjuvant treatment has not been shown to be effective in prolonging survival time.

A review of clinical trials suggests that no single method of treatment can efficiently address all variants of gastric cancer spread, and that no improvement in the results obtained in recurrence of gastric cancer can be expected. At present, therefore, prevention or reduction of the frequency of recurrence is probably more important than the early detection of recurrence.

Treatment should start with complete resection of the primary tumour, including an adequate resection margin and extended lymphadenectomy to reduce the incidence of locoregional failure. Based on the high rate of peritoneal recurrence in this study, surgery alone is seen to be an inadequate treatment for cure. The results of several randomized trials have demonstrated that intraperitoneal chemotherapy in normothermic or hyperthermic patients tends to improve survival rates and decrease the incidence of peritoneal failure compared with surgery alone[28–31]. For patients with a high risk of peritoneal recurrence, intraperitoneal chemotherapy may thus be a valuable adjuvant at operation or early in the postoperative period.

In conclusion, the patterns and timing of recurrence varied with the characteristics of primary gastric cancer. As the prognosis of patients with recurrence was very poor, the selection of postoperative adjuvant therapy in systemic (intravenous or intra-arterial) and/or regional (intraperitoneal) based on the predicted risk of each recurrence pattern may be a reasonable approach to improve the prognosis of gastric cancer.

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Original article

Surgical treatment for recurrent gastro-oesophageal reflux disease after failed antireflux surgery

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Background: Recurrent or persistent symptoms occur in 10–15 per cent of patients after antireflux surgery. Failure of surgery is not uniform in its presentation. The cause of failure is not easily detected and even harder to treat. Different approaches have been proposed and few reports are available on the objective and subjective outcome of reoperation.

Methods: This study focuses on 30 patients (16 men and 14 women; age range 20–69 years) with recurrent symptomatic gastro-oesophageal reflux disease (GORD) resistant to medical treatment. In all patients reoperation was by the Belsey Mark IV antireflux operation. A clinical history, endoscopy and oesophageal manometry were obtained in all patients, and 24-h pH monitoring was performed in 27 of 30 before and in most patients after the Belsey procedure.

Results: Symptomatic improvement was reported in 24 of 30 patients. Oesophagitis (present before operation in 19 patients) was cured or remained absent in 24 of 30 patients, stabilized in one, improved in four and deteriorated in one. Relief of symptoms combined with absence of oesophagitis was obtained in 21 of 30 patients, with concomitant normalization of the 24-h pH profile in 11 of 22 patients. The median basal lower oesophageal sphincter (LOS) pressure increased significantly from 6·9 to 9·0 mmHg ($P < 0·01$). Redo surgery had no effect on oesophageal body motility.

Conclusion: Reoperation performed for documented recurrent GORD had a good and lasting effect on symptoms, on oesophagitis (both in 24 of 30 patients) and on the combination of both (21 of 30). In these patients reoperation increased basal LOS pressure and decreased reflux time. Overall, the results approximate to those of primary operation.

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Introduction

Throughout the past decade antireflux surgery has gained renewed interest as an option for treatment of gastro-oesophageal reflux disease (GORD)[1,2]. Although current reports consistently indicate successful reflux control in 85–90 per cent of patients undergoing antireflux surgery, the operation fails in 10–15 per cent of patients because of recurrent reflux, dysphagia, 'gas bloat' syndrome or other complications[3–10]. Management of these patients poses a major clinical problem[11].

There is controversy on the cause of failure, the surgical approach, the type of reconstruction and the results[6,12–18]. Most studies focus on the subjective outcome of reoperation for a variety of indications after previous antireflux surgery[6,13–15,17,19]. Only a limited number of reports on the subjective and objective results of reoperation have been published[14,20–22]. In this paper, the subjective and objective results in patients undergoing a Belsey Mark IV reoperation for recurrent GORD only are described.

Patients and methods

Between 1982 and 1998, 30 patients had a Belsey Mark IV antireflux procedure because of recurrent GORD. The diagnosis of recurrent GORD was based on the combination of reflux symptoms (heartburn, regurgitation) with oesophagitis or pathological oesophageal acid exposure in 27 patients. In three patients, 24-h pH monitoring was not performed. Until the introduction of proton pump inhibitors (PPIs), patients were treated with a combination of H_2-receptor antagonists and prokinetic drugs (15 patients).

Since 1989, patients were treated with omeprazole 40–120 mg per day for at least 6 months, or with equivalent doses of other PPIs. All were persistently symptomatic on medical treatment and were referred for antireflux surgery.

A Belsey Mark IV antireflux procedure was performed in all patients, consisting of a 270° fundoplication with creation of a posterior buttress of the right crus through a left-sided thoracotomy in the sixth intercostal space[4,23]. All procedures were performed by the same two surgeons (J.L.T., H.G.G.). The operations performed before the Belsey procedure are listed in *Table 1*. In cases of oesophageal shortening, i.e. reconstruction under tension as judged at operation, a Collis gastroplasty was also performed to lengthen the oesophagus[24].

Reflux symptoms and endoscopy

Preoperative symptoms were scored according to a system combining frequency and severity[25]. For all questions related to heartburn, regurgitation and dysphagia as symptoms of GORD, severity (severe, moderate, mild or none) and frequency (daily, once a week, once a month, less than once a month) were scored. Heartburn was defined as any painful or burning sensation behind the sternum and/or subxiphoid region with or without relation to food intake and/or posture. Regurgitation was defined as any sensation of spontaneous eructation of gastrointestinal contents into the mouth or upper pharynx. Dysphagia was defined as an uncomfortable sensation of food sticking in the oesophagus shortly after or while eating. Data are presented as a composite score, i.e. as a combination of frequency and severity, and graded from 0 to 3.

Table 1 Primary antireflux procedures and subsequent operations performed in 30 patients

First operation	Second operation	Final operation
Nissen + HSV	Antrectomy/Roux–Y Antenor gastropexy	Belsey Mark IV (*n* = 7)
Nissen + HSV	Toupet	
Nissen	Belsey Mark IV	
Hill	Belsey Mark IV	
Boerema	Nissen (*n* = 2)	
Nissen	Nissen	
Nissen	Nissen	Collis–Belsey (*n* = 4)
Nissen	Belsey Mark IV	
Angelchik	Nissen	
Nissen (*n* = 9)		Belsey Mark IV (*n* = 19)
Nissen* (*n* = 6)		
Belsey Mark IV (*n* = 1)		
Hill (*n* = 2)		
Boerema (*n* = 1)		

*Six patients had a Nissen fundoplication with highly selective vagotomy (HSV) as the primary procedure

Endoscopic findings were graded according to the criteria of Savary and Miller[26]. The presence of Barrett's oesophagus was mentioned separately.

Oesophageal manometry and ambulatory pH monitoring

In all patients, oesophageal manometry was performed using a water-perfused catheter and a pneumohydraulic low-compliance perfusion system according to Arndorfer *et al.*[27]. Intraluminal oesophageal pressures in response to ten standardized wet swallows (10 ml water) were recorded at 5, 10 and 15 cm above the upper margin of the lower oesophageal sphincter (LOS). Peristaltic wave amplitude and duration of contraction were calculated for the proximal (15 cm above the LOS), mid (10 cm above the LOS) and distal (5 cm above LOS) part of the oesophagus. Peak-to-peak velocity of peristalsis for the proximal and distal part of the oesophagus was calculated. Thereafter, a pH glass electrode (model LOT440; Ingold, Urdorf, Switzerland) was positioned 5 cm above the manometrically determined upper margin of the LOS and connected to a digital datalogger, with a sampling rate of 0·2 Hz.

The reflux parameters were calculated for the 24-h data using a commercially available analysis program. Reflux parameters used in this study were percentage of time with pH less than 4 (total, upright, supine), number of reflux episodes (total, upright, supine) and mean duration of reflux episodes (total, upright, supine). All medication that could possibly interfere with the results was stopped at least 48 h before pHmetry. Twenty-four-hour pH monitoring data collected from 27 asymptomatic volunteers served as control values. Reflux was defined as pathological if the pH was below 4 for 4·0 per cent or more of the total time, 4·4 per cent or more of the time in the upright position and 1·2 per cent or more of the time in the supine position[28].

Definition of surgical outcome

Because 24-h pH monitoring was not possible in all patients, success was defined as relief of symptoms with documented absence of oesophagitis.

Vagal nerve integrity

In patients with symptoms suggestive of vagal nerve damage, plasma pancreatic polypeptide secretion in response to insulin hypoglycaemia was studied[29].

Statistical analysis

Symptom scores, pH monitoring data and oesophageal motility were expressed as median (range). The paired

Wilcoxon signed rank test was used for statistical analysis of symptom score and reflux variables from pHmetry. Statistical analysis of changes in basal LOS pressure was conducted by means of *t* tests for paired samples. All tests were performed using the statistical software package SPSS 7.5 for Windows (SPSS, Chicago, Illinois, USA). The significance level was set at $P < 0{\cdot}05$.

Results

There were 16 men and 14 women (median age 48 (range 0–69) years). Median postoperative hospital stay was 11 (range 6–24) days. Follow-up after the final reoperation ranged from 0·5 to 13 (median 6) years. The suggested causes of technical failure of previous antireflux operations, observed during the Belsey Mark IV operation, are presented in *Table 2*.

Postoperative complications

In-hospital and late complications are presented in *Table 3*. There were no deaths. Perioperative complications were seen in eight patients and were all treated successfully without lasting consequences. Late complications occurred in 11 patients. Recurrent reflux symptoms occurred in two patients; one had persisting reflux symptoms after reoperation in combination with complaints of delayed gastric emptying, based on documented vagal nerve damage. Another patient was initially free of reflux symptoms but heartburn recurred after 3 years and oesophagitis grade II was seen on endoscopy. Four patients developed dyspeptic symptoms without symptoms of GORD. This could be explained by delayed gastric emptying of solid food. In these patients vagal nerve damage was diagnosed, in two of whom vagal nerve damage was already present before reoperation. Two of these four patients underwent a B1 partial gastrectomy and the other two were treated satisfactorily with prokinetic drugs. 'Post-thoracotomy' syndrome was seen in four patients and was treated successfully with a combination of physiotherapy and intercostal analgesic injections in three.

Table 2 Suggested cause of failure of previous antireflux operations in 30 patients undergoing a Belsey Mark IV or Collis–Belsey operation

Cause of failure	No of patients
Diaphragmatic hernia	3
Inadequate fundoplication	19
Fundoplication too loose	1
'Stomach-around-stomach'	4
No fundoplication found	7
Minor remnants of fundoplication	7
Dislocation of the fundoplication	6
Paraoesophageal hernia	1
'Slipped Nissen'	2
Partial herniation of fundoplication into thorax	3
Unknown	2

Effect of operation on symptoms

The operation reduced the composite score for heartburn from 3 (1–3) to 0 (0–2) ($P < 0{\cdot}001$) and for regurgitation from 2 (0–3) to 0 (0–2) ($P < 0{\cdot}001$). The effect of surgery on heartburn and regurgitation in individual patients is shown in *Figs 1* and *2*. Considering this group of patients as a whole, dysphagia was not a prominent symptom before reoperation and the dysphagia score was not affected by the final operation. Twenty-four of 30 patients (80 per cent) had no or minimal symptoms after reoperation and the operation was judged to be successful overall.

Effect of operation on endoscopic findings

The effect of reoperation on endoscopic findings is presented in *Fig. 3*. Before reoperation, 11 patients had no signs of oesophagitis. In these 11 and in 13 other patients, there was no oesophagitis after reoperation. After reoperation oesophagitis was reduced to grade 1 in four patients, deteriorated in one and stabilized in another patient. A reduction in oesophagitis score from 1 (0–4) before to 0

Table 3 Perioperative and late complications in 30 patients after Belsey Mark IV procedure

Complication	Treatment	No of patients
Perioperative complications		
Gastrointestinal bleeding	Reoperation	2
Viral pericarditis	Puncture	1
Extrapleural effusion	Drainage	1
Impaction of food bolus	Endoscopic removal	1
Urinary tract infection	Antibiotics	1
Pulmonary infection	Antibiotics	2
Late complications		
Recurrent reflux disease	Medication	2†‡
Dysphagia	Dilatation	1
Delayed gastric emptying*	Medication ($n=2$) B1 partial gastrectomy (and Roux-Y) ($n=2$)	4†§
Osteochondritis	Excision costal cartilage	1
Post-thoracotomy pain	Intercostal blockade	4‡§
Calcification in midline laparotomy	Excision	1
Cicatricial hernia of midline laparotomy	Operation	1

*Based on vagal nerve damage, diagnosed with pancreatic polypeptide stimulation test. †‡§Each symbol indicates a patient with more than one complication

(0–2) ($P<0{\cdot}001$) after reoperation was observed. Five patients had a Barrett segment on preoperative endoscopy, in combination with oesophagitis in three. Although the Barrett segment persisted after operation, concomitant oesophagitis had healed.

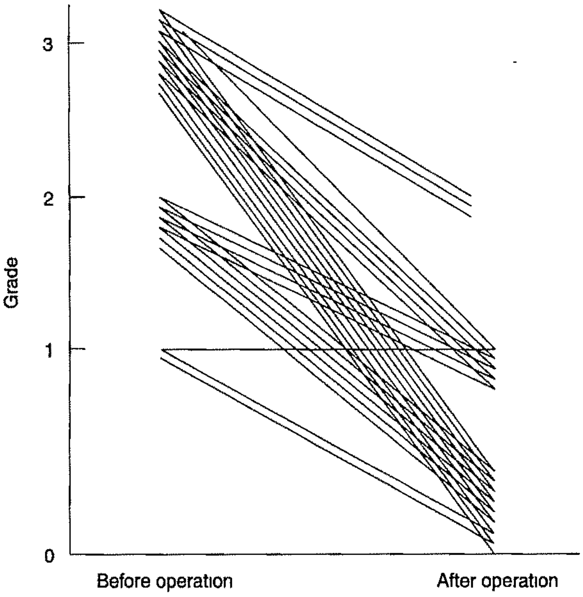

Fig. 1 Effect of reoperation on heartburn in patients with recurrent gastro-oesophageal reflux disease ($n=30$). $P<0{\cdot}001$, Wilcoxon signed rank test

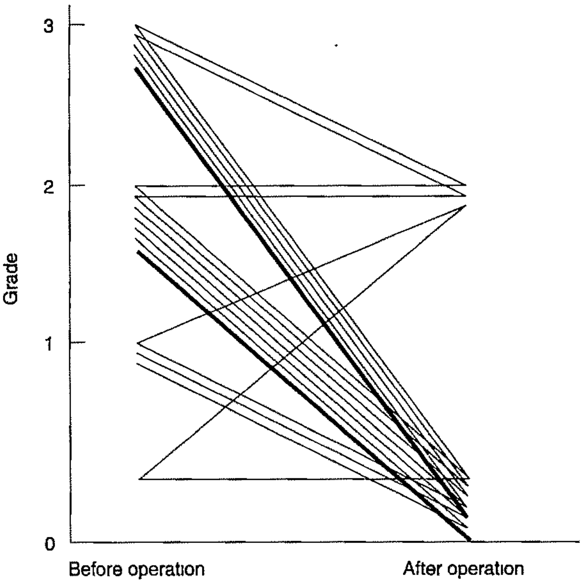

Fig. 2 Effect of reoperation on regurgitation in patients with recurrent gastro-oesophageal reflux disease ($n=30$). $P<0{\cdot}001$, Wilcoxon signed rank test

Effect of operation on lower oesophageal sphincter characteristics and oesophageal body motor function

The basal LOS pressure was low before operation and increased significantly from 6·9 (0·8–15·0) to 9·0 (2·3–20·0) mmHg ($P=0{\cdot}001$). The intra-abdominal length of the high-pressure zone was not significantly different before and after operation: 2·0 (0·5–5·0) and 2·2 (1·0–3·8) cm. Oesophageal body motor function was not affected by reoperation.

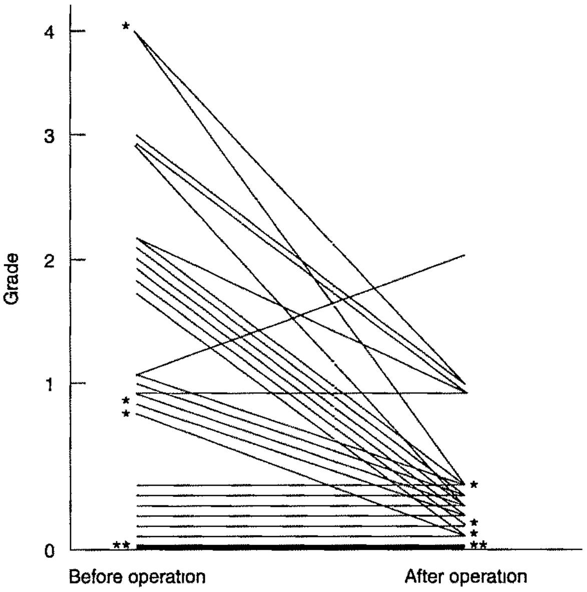

Fig. 3 Effect of reoperation on endoscopic findings in patients with recurrent gastro-oesophageal reflux disease ($n=30$). *Patients with a Barrett segment that persisted after reoperation. $P<0{\cdot}001$, Wilcoxon signed rank test

Table 4 Effect of reoperation (Belsey Mark IV) on 24-h pH profile in 22 of 30 patients with recurrent gastro-oesophageal reflux disease

	Before reoperation	After reoperation
Reflux (% of time)		
Total	15·0 (2·0–66·3)	2·3 (0·0–21·5)*
Upright	14·8 (0·1–71·0)	2·7 (0·0–27·0)*
Supine	14·0 (0·0–77·3)	1·0 (0·0–37·9)†
No. of episodes		
Total	86 (20–546)	19 (0–209)*
Upright	75 (11–391)	11 (0–148)*
Supine	17 (0–155)	2 (0–73)‡

Values are median (range). *$P<0{\cdot}001$, †$P=0{\cdot}015$, ‡$P=0{\cdot}012$ *versus* before reoperation (Wilcoxon signed rank test)

Effect of operation on 24-h pH profile

Table 4 shows the effect of reoperation on 24-h pH recording. Preoperative and postoperative 24-h pH data were available for 22 of 30 patients. Preoperative measurements were not available for three patients owing to refusal, use of a PPI and technical problems. After reoperation, five patients refused further screening since they were asymptomatic. Endoscopy showed no signs of oesophagitis or Barrett's oesophagus in these patients. The total percentage of reflux time decreased significantly ($P < 0.001$) in 20 of 22 patients, but normalization of the 24-h pH profile, defined as less than 4·0 per cent of the total time with pH below 4[28], was obtained in only 13 of 22. The number of reflux episodes decreased significantly as well. For clearance, there was no significant difference.

Effect of operation on combined, subjective and objective, outcome

Based on the postoperative absence of oesophagitis, 24 of 30 patients had a successful outcome. According to the definition of success used in this study, 21 of the 30 patients had a successful reoperation.

Discussion

The proportion of patients requiring a revisional procedure after antireflux surgery is estimated to be about 3–6 per cent[5,11,15,22]. The indication for reoperation has not changed essentially over the past 15 years, although since the introduction of PPIs more patients respond sufficiently to medical treatment[1,2,30]. Since regurgitation usually responds less well to medical treatment than heartburn, it is not surprising that regurgitation was present in 17 of 30 patients.

Although the cause of failure is not always easy to detect, Stein *et al.*[5] reported that 50 per cent of failed antireflux procedures were due to technical failure or to inappropriate patient selection. The main causes of technical failure are disruption of the initial antireflux repair or displacement of the fundoplication, sometimes owing to shortening of the oesophagus[3,5,6,12–14,20,31]. In more than half of the present patients no or only limited remnants of the wrap were found at reoperation. In two of the three repeat Belsey procedures, the second row of stitches had torn out. Since repositioning was easy, oesophageal shortening was apparently not the cause of failure in these patients. Displacement of the fundoplication into the thorax may be caused by oesophageal shortening and is best dealt with by a left-sided thoracotomy[16,17]. There are, however, no solid preoperative criteria by which to identify oesophageal shortening and to determine the need for a Collis gastroplasty[24].

Selection of the appropriate surgical approach for redo surgery remains controversial and is usually based on personal experience with one standard technique[5,12,18,21]. In order to adopt a uniform strategy in recurrences, a left-sided thoracotomy with a 270° fundoplication was performed in all of these patients, because it is preferable to use a previously unoperated route[13] (the gastro-oesophageal hiatus can be explored by thoracotomy[12,16,17,27] as well as by (re)laparotomy[20,32]) and because a thoracic approach leaves the option of entering the abdomen through the muscular part of the diaphragm, whereas a laparotomy cannot easily be converted to a thoracotomy[16,18]. In four patients a combined procedure like Collis–Belsey was performed to compensate for oesophageal shortening. Otherwise, reposition of the wrap without tension was impossible. The postoperative LOS characteristics indicate that it was possible to restore a lasting, intra-abdominal segment of high pressure, which is an indirect sign of an oesophagus with sufficient length.

Although these results with a thoracic approach as the standard procedure are satisfactory and the technical problems were solved, this approach is not always necessary in cases where there is no doubt that the sphincter is localized well below the diaphragm. Given the diversity of technical failures of previous operations in this series and the need to perform a Collis–Belsey procedure in four patients, the authors feel confident about the transthoracic approach as the standard procedure for reoperation. This study confirms that, despite the technically higher degree of complexity, success rates of redo antireflux surgery are satisfactory. The morbidity rate, however, is higher and must be considered when discussing surgery with these patients. The present results compare favourably to those of other authors who report good to excellent results in about 65–85 per cent of patients[5,6,12–14,16,18,20]. Little *et al.*[17] have noted that the results deteriorate with increasing number of operations because of impaired oesophageal function and progressive tissue destruction. The present series is smaller than theirs and their findings could not be confirmed since disorders of oesophageal body motor function were not detected either before or after reoperation. The current findings are in line with those described in a previous study on oesophageal body motility after the Belsey Mark IV procedure[33].

Reoperation for recurrent reflux led to symptomatic relief in 24 of 30 patients, with concomitant healing of oesophagitis in 21 of the 30 patients. In four of the six symptomatic patients, reflux and dyspeptic symptoms were influenced by disturbed gastric motor function. Two of these already had vagal nerve damage before the Belsey Mark IV reoperation, and further deteriorated afterwards. Post-thoracotomy pain is the drawback of an otherwise successful therapy and is not always easy to treat. The subjective and objective results in this series are comparable to those obtained in a series of primary antireflux procedures with a similar follow-up time, in which successful symptomatic relief and healing of oesophagitis occurred in 87 per cent of patients[34].

Reoperation decreased the total acid exposure of the oesophageal mucosa, but in nine of 22 patients acid exposure did not normalize. Only two of these nine patients, however, were symptomatic. These results are in line with those obtained in other series. Feussner *et al.*[35] also observed pathological reflux after refundoplication in 10 per cent of patients postprandially and in 20 per cent in the fasting upright position. Luostarinen *et al.*[22] reported 40 per cent recurrent reflux in asymptomatic patients after Nissen refundoplication.

In conclusion, objective and subjective success of redo antireflux surgery with the use of the Belsey Mark IV procedure was observed in this study. The results of reoperation were found to be nearly as good as those of primary surgery.

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Errata

H. Nishio, J. Kamiya, M. Nagino, M. Kanai, K. Uesaka, E. Sakamoto, T. Fukatsu and Y. Nimura. Value of percutaneous transhepatic portography before hepatectomy for hilar cholangiocarcinoma. *Br J Surg* 1999; **86**: 1415–1421.
The horizontal-axis label on *Fig. 6* should read 'Time (years)'.
The second last sentence of Results should read 'Numbers of 1-, 3- and 5-year survivors of the 25 patients were 15, three and one respectively, and the median survival was 18·1 months'.

C. Norton and M. A. Kamm. Outcome of biofeedback for faecal incontinence. *Br J Surg* 1999; **86**: 1159–1163.
The final row in *Table 2* should read as follows:

	Cured	Improved	No change
Both sphincters abnormal (*n*=27)	7	5	15

Referee index. *Br J Surg* 1999; **86**: 1614–1616.
Mr H. Gajraj was erroneously omitted from this list.

The Journal apologizes for these errors.

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

Bacterial infection and extent of necrosis are determinants of organ failure in patients with acute necrotizing pancreatitis

Sir

This important paper by Isenmann *et al.* (*Br J Surg* 1999; **86:** 1020–4) demonstrates an association between bacterial infection of pancreatic and peripancreatic necrosis and organ failure in patients with acute pancreatitis. These authors have previously demonstrated that the incidence of positive cultures is influenced by the interval from disease onset to sampling[1]. Thus, for the correct interpretation of their data in the present study, information on delay to sampling is mandatory. In particular, it is possible that patients in group 1 (less than 30 per cent necrosis) were sampled at an earlier stage in their disease course and they may also have had a higher proportion of fine-needle aspiration cytology diagnoses. From the data presented, it is not possible to exclude differential sampling intervals as an explanation of the apparent difference in the incidence of infected necrosis.

A second point is that the results are critically dependent on the definition of the study population. The authors studied 300 consecutive patients with necrotizing pancreatitis treated during a 14-year period. However, unless all patients with acute pancreatitis underwent computed tomography, it is possible that patients with lesser degrees of necrosis were undetected. The relatively high proportion of patients with organ failure in this study (78 per cent) may thus result from sampling bias towards the more severe end of the disease spectrum. Differential detection and inclusion of such patients may, in part, be responsible for the reported discrepancies in outcome between patients with infected and sterile necrosis to which the authors allude. The development of reliable serum markers of pancreatic necrosis or the use of polymerase chain reaction methods to detect and quantify the presence of pancreatic bacterial-derived DNA may in future allow larger populations of patients to be sampled.

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1 Beger H, Bittner R, Block S, Buchler M. Bacterial contamination of pancreatic necrosis. A prospective clinical study. *Gastroenterology* 1986; **91:** 433–8.

Authors' reply

Sir

Messrs Beattie and Siriwardena have raised several questions concerning our paper. The first concerns a potential bias presumably caused by differences in the sampling period of bacterial smears from pancreatic necrosis. Checking our data revealed the following: in patients with infected pancreatic necrosis, bacterial infection was proven after a median of 14·3 days in group 1, 18 days in group 2 and 18·5 days in group 3. Statistically, these differences were not significant. The proportion of fine-needle aspiration cytologies was similar in all three groups: 25 per cent of patients in group 1, 50 per cent in group 2 and 45 per cent in group 3. Again, the differences were not significant. The lower number of biopsies in group 1 can be explained by the fact that this invasive method was only performed when pancreatic infection was suspected by clinical and laboratory criteria.

The second point is the fear that patients with minor necrosis might have been undetected, which would lead to a bias of the results towards the severe end of the spectrum. We, together with others[1–3], rely on the high diagnostic accuracy of serum markers of necrosis (C-reactive protein and lactate dehydrogenase) in identifying patients with pancreatic necrosis. Patients with acute pancreatitis were carefully monitored for a raise in these markers during the early phase and contrast-enhanced computed tomography (CT) was performed whenever they indicated necrotizing pancreatitis. All data of our present study are based on CT findings. We cannot exclude the fact that a small proportion of patients with minor pancreatic necrosis following an uneventful course were not diagnosed correctly as having necrotizing pancreatitis and would have been missed for evaluation. We do not think that this will have influenced our data. We share the opinion that there is a need for evaluation of new markers of pancreatic necrosis and especially for the early detection of pancreatic infection.

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1 Wilson C, Heads A, Shenkin A, Imrie CW. C-reactive protein, antiproteases and complement factors as objective markers of severity in acute pancreatitis. *Br J Surg* 1989; **76:** 177–81.
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Oral nifedipine reduces resting anal pressure and heals chronic anal fissure

Sir

We read with interest the article by Cook *et al.* (*Br J Surg* 1999; **86**: 1269–73) who assessed the effectiveness of nifedipine retard 40 mg daily over a 5-day period in healing chronic anal fissure. Healing was complete in nine patients and symptomatic improvement was documented in a further three. On the basis of these results, the authors state that nifedipine offers an alternative means to treat chronic fissure. We think that a follow-up period of 3 months is not long enough and believe that 93 per cent is a high rate of side-effects. It is likely that flushing and mild headache interfered with the quality of life of the patients.

Botulinum toxin injection is more effective in inducing fissure healing than other therapies[1]. The injection is not related to the patient's willingness to complete treatment, it is effective in alleviating sphincter hypertonia and no complications or side-effects were reported either after injections or during the follow-up period[1–3].

In patients with posterior anal fissure, we found a healing rate of 96 per cent when botulinum toxin was injected anteriorly into the internal sphincter. The different injection site induces a greater decrease in resting pressure and improves the clinical outcome. This effect should be related to fibrosis of the internal sphincter that is more prominent at the site of the fissure than at other sites in the smooth muscle[4]. The fibrosis may reduce the compliance of the internal sphincter and limit the diffusion of the toxin.

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2 Maria G, Cassetta E, Gui D, Brisinda G, Bentivoglio AR, Albanese A. A comparison of botulinum toxin and saline injection for treatment of chronic anal fissure. *N Engl J Med* 1998; **338**: 217–20.
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4 Brown AC, Sumfest JM, Rozwadowski JV. Histopathology of the internal anal sphincter in chronic anal fissure. *Dis Colon Rectum* 1989, **32**: 680–3.

Authors' reply

Sir

We thank Drs Brisinda and Maria for their interest in our article. Although the minimum follow-up period of 3 months was short, initial healing rates with oral nifedipine were encouraging. Only ten patients experienced side-effects, although some experienced both flushing and mild headache. These adverse effects were primarily in the initial treatment period and subsided with time. We did not assess quality of life but the side-effects were short-lasting and did not prevent participants from performing daily activities. The rapid reduction in pain with nifedipine treatment is likely to have resulted in an overall improvement in quality of life.

Brisinda and Maria had few adverse effects using botulinum toxin but transient faecal incontinence in 7 per cent of patients[1] and perianal thrombosis have been described[2]. Patients may require repeated treatment and the long-term effects of injections into the internal anal sphincter have yet to be assessed. As stated, comparison of healing rates with other series was difficult because seven patients had previously failed treatment with glyceryl trinitrate. The results following botulinum toxin injection are encouraging but medication by mouth is acceptable and avoids the trauma of injection. We believe the early results of oral nifedipine are promising and merit further investigation.

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1 Jost WH One hundred cases of anal fissure treated with botulin toxin: early and long-term results. *Dis Colon Rectum* 1997; **40**: 1029–32.
2 Jost WH, Schanne S, Mlitz H, Schimrigk K. Perianal thrombosis following injection therapy into the external anal sphincter using botulin toxin. *Dis Colon Rectum* 1995; **38**: 781 (Letter).

Bilirubin and peripheral vascular disease

Sir

Dr Kangas and colleagues (*Br J Surg* 1999; **86**: 713) report no significant difference in serum bilirubin concentrations between controls ($n = 30$) and patients with peripheral vascular disease (PVD) ($n = 30$). The bilirubin levels were 30 per cent higher in controls (13 *versus* 10 μmol/l) and this trend may achieve significance in a larger study which would then support a link between reduced bilirubin levels and the extent of arterial disease, as proposed by others[1–3].

The conclusions made by Kangas *et al.* are considerably limited because they pooled men and women and did not consider smokers separately. It is well established that women and smoking are associated with lower bilirubin levels in healthy subjects[2,3].

We studied asymptomatic dyslipidaemic patients: male non-smokers ($n = 119$) had significantly higher bilirubin levels than male smokers ($n = 36$) (mean 9·9 *versus* 8·2 µmol/l, $P = 0{\cdot}02$, Mann–Whitney U test) or female non-smokers ($n = 118$) (8·5 µmol/l, $P = 0{\cdot}004$). In patients with PVD, a similar trend was seen with smoking and gender (male non-smokers ($n = 42$) 9·1 µmol/l *versus* male smokers ($n = 31$) 6·9 µmol/l ($P = 0{\cdot}02$) *versus* female non-smokers ($n = 29$) 7·6 µmol/l ($P = 0{\cdot}12$)). These findings indicate that the effect of gender and smoking on bilirubin levels is also relevant in patients with dyslipidaemia or PVD.

The role of bilirubin as a marker or predictor of vascular disease has yet to be established. This question can only be answered by large studies and not by limited observations such as those from Kangas *et al.*

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1 Schwertner HA, Jackson WG, Tolan G. Association of low serum concentration of bilirubin with increased risk of coronary artery disease. *Clin Chem* 1994; **40:** 18–23.

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Book reviews

Prognosis and Outcomes in Surgical Disease

D. P. McKeller, R. B. Reiling and B. Eiseman (eds).

215 × 278 mm. Pp 465 Illustrated 1999. St Louis, Missouri. Quality Medical Publishing $85

This book has evolved from an innovative publication in 1980 entitled *Prognosis of Surgical Disease*. A diagrammatic approach throughout this textbook (diagrams on the right page and comments on the left page) is a follow-up of Eiseman's surgical decision-making book of 1978. The intended audience is general surgeons, residents and family practitioners, and the purpose is efficiently to provide information for patients of expected outcomes, with the use of simple diagrams. The authors, mainly from the USA using literature updated to 1998, have succeeded in terms of uniformity with a focus on outcome results. Clinical decisions should depend on treatment performance measured by sensitivity, specificity and predictive values; these are what the authors have used throughout this volume on a wide range of surgical diseases. As opposed to previous volumes there now is a much better focus on the literature on which the presented diagrams are based. Unfortunately, not all literature is of the same scientific (preferably trial based) level.

More and more the public asks to be involved in the decision-making process, especially in the matter of comparing the different treatment options. For this, the book is excellent and no comparable surgical textbook exists. It is certainly helpful in providing a quick reference work for most surgical problems, with a knowledgeable approach to surgical decision making. Obviously, the literature used per section is limited (on average not more than 30 references), but it represents the most current prospective data. This reference book is highly recommended for the intended audience but it will require regular revision every few years.

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Endovascular Intervention: Basic Concepts and Techniques

F. J. Criado (ed.)

287 × 220 mm Pp 190. Illustrated 1999. Armonk, New York Futura Publishing Company. $79.

This book is a practical manual of basic endovascular intervention aimed at vascular surgeons requiring an endovascular upgrade. The most useful chapters covering wires and catheters, percutaneous puncture, and diagnostic angiography are very well written and illustrated. Other chapters on endovascular suite design, the biomechanics of stents and the metallurgical properties of nitinol could have been omitted without any great loss to the purpose of the book. The remainder of the volume covers intervention in specific areas chapter by chapter (iliac, femoropopliteal, tibial, carotid, renal, subclavian) and considers stent grafting of aneurysms and thrombolysis. The emphasis on basic skills is less evident in these chapters which rely more on a description of techniques. I was looking for lists of common problems, what to do when in trouble, how to get out of trouble, but these topics were not covered in quite the depth a beginner might require. My other slight criticism was the emphasis on stents for most lesions which is certainly not evidence based. There is undoubtedly a need for a good endovascular instruction manual and parts of this book fulfil this role. Vascular surgeons and trainees will find it a useful starting point for their endovascular training.

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Scientific Surgery

Temple LKF, Litwin DE, McLeod RS A meta-analysis of laparoscopic *versus* open appendectomy in patients suspected of having acute appendicitis. *Can J Surg* 1999; **42**: 377–83.

Twelve studies were included. Laparoscopic surgery took longer, did not affect duration of hospital stay, but return to normal activities was accelerated

Melissano G, Blasi F, Esposito G, Tarsia P, Dordoni L, Arosio C *et al. Chlamydia pneumoniae* eradication from carotid plaques. Results of an open randomised treatment study. *Eur J Vasc Endovasc Surg* 1999; **18**: 355–9.

Patients were randomized to a 1-month course of roxithromycin or no treatment before carotid surgery Chlamydia was subsequently detected in the excised carotid plaque in five of 16 treated patients and 12 of 16 controls (P=0·034)

Ihlberg L, Luther M, Alback A, Kantonen I, Lepantalo M. Does a completely accomplished duplex-based surveillance prevent vein graft failure? *Eur J Vasc Endovasc Surg* 1999; **18**: 395–400.

This trial included 362 patients but focused on those who attended all their surveillance scans Twelve-month secondary patency rates were similar after duplex (83 per cent) and ankle pressure based follow-up (87 per cent)

Sietses C, Wiezer MJ, Eijsbouts OA, Beelen RH, van Leeuwen PA, von Blomberg BM *et al.* A prospective randomized study of the systemic immune response after laparoscopic and conventional Nissen fundoplication. *Surgery* 1999, **126**: 5–9.

In this study including 17 patients, activation of the systemic immune response was detected in all patients, but was greater after conventional surgery

Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari L. Subtotal *versus* total gastrectomy for gastric cancer: five year survival rates in a multicentre randomized Italian trial. *Ann Surg* 1999; **230**: 170–8.

Some 618 patients were randomized. Five-year survival was similar 65 per cent after subtotal and 62 per cent after total gastrectomy, but nutritional status and quality of life were better preserved after subtotal gastrectomy

Johansson B, Hallerback B, Glise H, Anesten B, Smedberg S, Roman J. Laparoscopic mesh *versus* open preperitoneal mesh *versus* conventional technique for inguinal hernia repair: a randomized multicentre trial (SCUR Hernia Repair Study). *Ann Surg* 1999; **230**: 225–31.

Some 613 patients were included Laparoscopic mesh repair resulted in a shorter time to full recovery and return to work, but had a higher complication rate and was significantly more expensive Recurrence rates were similar

Kennedy ML, Sowter S, Nguyen H, Lubowski DZ. Glyceryl trinitrate ointment for the treatment of chronic anal fissure: results of a placebo-controlled trial and long-term follow-up. *Dis Colon Rectum* 1999; **42**: 1000–6.

Forty-three patients were randomized GTN reduced resting anal pressures and pain scores, and resulted in a significantly better fissure healing rate (46 *versus* 16 per cent, P=0·001)

Antropoli C, Perrotti P, Rubino M, Martino A, DeStefano G, Migliore G *et al.* Nifedipine for local use in conservative treatment of anal fissures: preliminary results of a multicentre study. *Dis Colon Rectum* 1999; **42**: 1011–15.

A total of 283 patients were included After 21 days, total remission from fissure was achieved in 95 per cent after nifedipine *versus* 50 per cent after placebo (P<0·01) Nifedipine reduced resting anal pressure by 30 per cent

Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon ATR. Non-pathogenic *Escherichia coli versus* mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet* 1999; **354**: 635–9.

Some 116 patients with active colitis were studied. In addition to standard medical therapy, *E coli* was as effective as mesalazine in attaining remission (68 *versus* 75 per cent) and in preventing relapse (67 *versus* 73 per cent)

Dale JJ, Ruckley CV, Harper DR, Gibson B, Nelson EA, Prescott RJ. Randomised double blind placebo controlled trial of pentoxifylline in the treatment of venous leg ulcers. *BMJ* 1999; **319**: 875–8.

Complete ulcer healing was not statistically significantly improved in patients receiving pentoxifylline (64 *versus* 53 per cent in patients on placebo) in this study including 200 patients

Abu Galala KH, Salam IM, Abu Samaan KR, El Ashaal YI, Chandran VP, Sabastian M *et al.* Treatment of pilonidal sinus by primary closure with a transposed rhomboid flap compared with deep suturing. a prospective randomised clinical trial. *Eur J Surg* 1999; **165**: 468–72.

Rhomboid flap repair was superior in this study of 43 patients: primary healing was improved (100 *versus* 77 per cent) and after a mean of 18 months there were fewer recurrences (none *versus* two).

Zieren J, Zieren HU, Jacobi CA, Muller JM. Repeated boluses of local anaesthetic for pain relief after inguinal hernia repair. *Eur J Surg* 1999; **165**: 460–4.

There was no advantage to bolus injections of bupivacaine through a subcutaneous catheter into the wound There was no improvement in pain scores or analgesic requirements compared with a control group in this trial including 104 patients.

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Use abbreviations *sparingly* Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension. Abbreviations must be used consistently and must be defined on first use.

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Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value. Actual *P* values should be reported to two decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

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